Synthesis and biological activity of isogranulatimide analogues

Bernadette Hugon, Fabrice Anizon, Christian Bailly, Roy Golsteyn, Alain Pierré, Stéphane Leonce, John Hickman, Bruno Pfeiffer, Michelle Prudhomme

Synthesis and biological activities of isogranulatimide analogues

Bernadette Hugon,[a] Fabrice Anizon,[a] Christian Bailly,[b] Roy M. Golsteyn,[c] Alain Pierré,[c] Stéphane Léonce,[c] John Hickman,[c] Bruno Pfeiffer[c] and Michelle Prudhomme[a,*]

[a]*Laboratoire SEESIB, Université Blaise Pascal, UMR 6504 du CNRS, 63177 Aubière, France*
[b]*INSERM U-524 et Laboratoire de Pharmacologie Antitumorale du Centre Oscar Lambret, 59045 Lille, France*
[c]*Institut de Recherches SERVIER, Division Recherche Cancérologie, 125 Chemin de ronde, 78290 Croissy sur Seine, France*

Abstract—The synthesis of new isogranulatimide analogues, their inhibitory activities toward the Checkpoint 1 kinase (Chk1), and their in vitro cytotoxicities toward four tumor cell lines (one murine L1210 leukemia, and three human cell lines: DU145 prostate carcinoma, A549 non-small cell lung carcinoma, and HT29 colon carcinoma) are described. The affinity for DNA of some representative compounds and their ability to induce DNA cleavage mediated by topoisomerase I have been examined. In some of the newly synthesized compounds, the imidazole heterocycle of isogranulatimide is replaced by a pyrrole and/or the indole unit is replaced by a 7-azaindole. Compounds in which a sugar part is attached to the 7-azaindole moiety have also been prepared. Some of the newly synthesized compounds are more potent Chk1 inhibitors than granulatimide. The selectivity of two potent Chk1 inhibitors **24** and **26** has been evaluated using various kinases. The strongest inhibitory properties are found toward Chk1.

1. Introduction

To ensure the fidelity of division of a single cell to yield two daughter cells, several checkpoints in the cell cycle may be activated in response to DNA damage. The cellular response to DNA damage involves cell cycle delays, increased repair, and apoptosis.[1–4]

Genetic instability is a hallmark of virtually all tumors. Most of the tumor cells have a defect in the G1/S checkpoint that causes the tumor cells to be more dependent on the G2 checkpoint in response to DNA damage. Abrogation of the G2 checkpoint in the presence of DNA-damaging agents can lead to mitotic catastrophe in the tumor cells. The checkpoints are controlled by ATR and ATM central proteins. Activation of ATR induces activation of the Checkpoint 1 kinase (Chk1).[5] Inhibition of Chk1 provides an attractive opportunity to abrogate the G2 checkpoint and to enhance toxicity of genotoxic drugs selectively in cancer cells.[6,7]

Keywords: Isogranulatimide; Chk1 inhibitors; Pyrrolo[3,4-*c*]carbazole; Antitumor drugs.
* Corresponding author. Tel.: +33 4 73 40 71 24; fax: +33 4 73 40 77 17; e-mail: Michelle.PRUDHOMME@univ-bpclermont.fr

Among the known G2 checkpoint abrogators are UCN-01, granulatimide, and isogranulatimide which have been isolated from the ascidian *Didemnum granulatum*. They inhibit the G2 checkpoint with IC_{50} values of 0.06, 2, and 3 μM, respectively, and Chk1 with IC_{50} values of 0.007, 0.25, and 0.1 μM, respectively (Fig. 1).[8–13]

Analogues of granulatimide and isogranulatimide have been synthesized with the aim of obtaining more efficient compounds.[12–19]

In this paper, we report the synthesis of isogranulatimide analogues in which the imidazole heterocycle has been replaced by a pyrrole and/or in which the indole moiety has been replaced by a 7-azaindole. Since UCN-01 bears a carbohydrate part, we have also synthesized, in 7-azaindole series, analogues **44** and **45** possessing a sugar moiety (Fig. 2). The sugar unit may form additional hydrogen bonds in the ATP-binding site of the kinase and/or may induce topoisomerase I-mediated DNA strand breaks as do rebeccamycin (Fig. 2), a microbial metabolite isolated from cultures of *Saccharothrix aerocolonigenes*. The antitumor activity of rebeccamycin is linked to its capacity to inhibit topoisomerase I by forming a ternary complex DNA-topoisomerase I-rebeccamycin that prevents the religation of the cleaved DNA strand.[20–22] We have showed

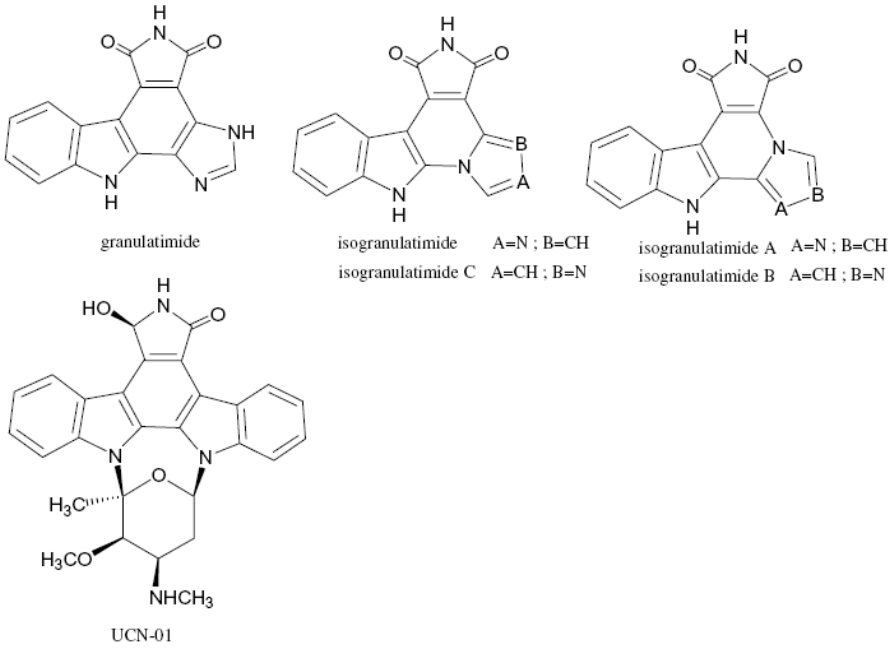


Figure 1. Chemical structures of well-known Chk1 inhibitors.

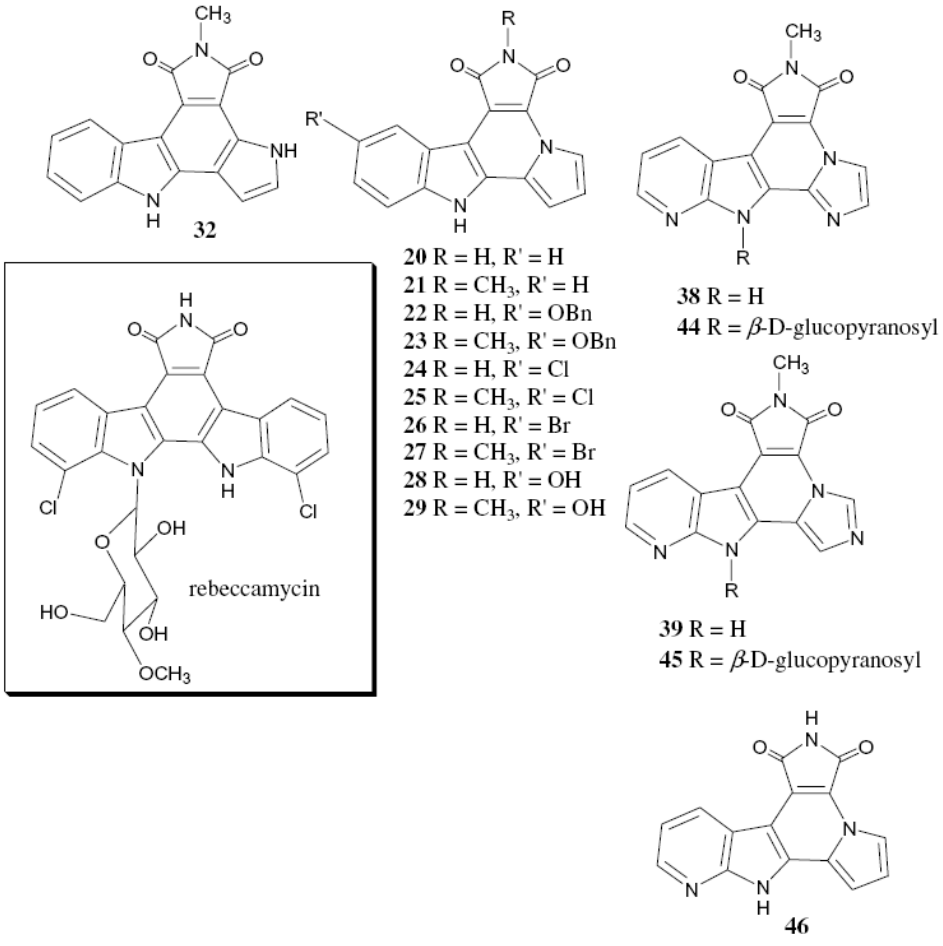


Figure 2. Structures of rebeccamycin and compounds described in this study.

that the sugar residue attached to the indolocarbazole chromophore is critical for the drug's ability to interfere with topoisomerase I as well as for the formation of intercalation complexes. The indolocarbazole chromophore is oriented parallel to the base pair plane of DNA whereas the carbohydrate interacts with the grooves.

The Chk1 inhibitory properties of the newly synthesized compounds have been determined and compared with those of granulatimide and isogranulatimide. To get an insight into the kinase selectivity of this family of compounds, the percentages of activity of various kinases [Checkpoint 1 kinase (Chk1), AMP-activated protein kinase (AMPK), Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII), casein kinase I (CKI), fibroblast growth factor receptor 3 (FGFR3), glycogen synthase kinase 3 (GSK3), lymphocyte-specific protein tyrosine kinase (LCK), MAP kinase 1 (MAPK1), mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2), kinase responsible for site specific phosphorylation of BAD (P70S6K), protein kinase A (PKA), protein kinases C β, α, ε isoforms (PKCβ, PKCα, PKCε)] in the presence of two compounds **24** and **26** at a concentration of 1 μM were evaluated. The inhibitory activities of the most potent Chk1 inhibitors **20**, **24**, **26**, **28** toward Src tyrosine kinase were also determined.

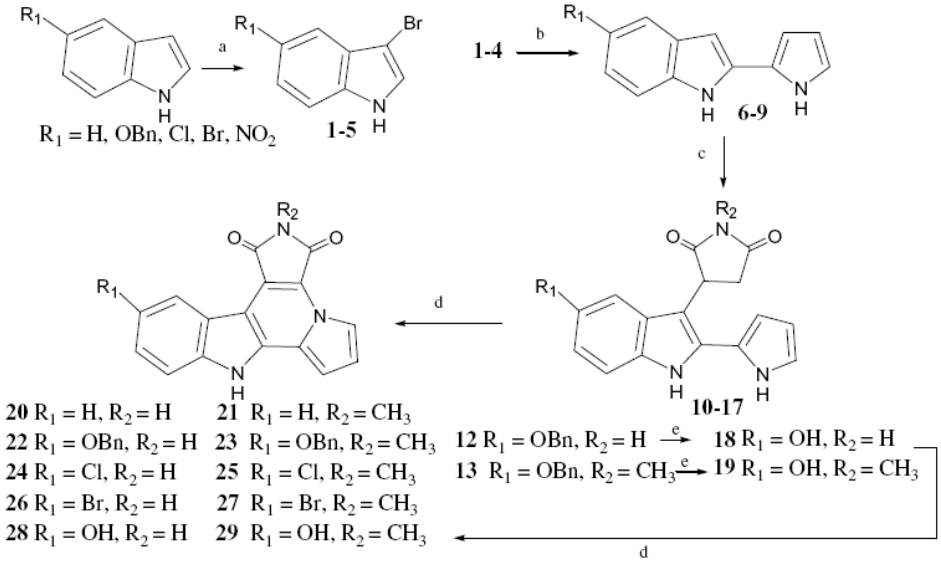
The in vitro antiproliferative activities against four tumor cell lines: murine leukemia L1210, and human DU145 prostate carcinoma, A549 non-small cell lung carcinoma, and HT29 colon carcinoma were evaluated. DNA interaction of the some representative compounds in the presence or the absence of topoisomerase I was investigated and the results are reported.

2. Results and discussion

2.1. Chemistry

In previous brief communications, we described the access to pyrrolic compounds **20**–**29** and to imidazolic compounds **38**, **39**, **44**, **45**.[16,17] Another pyrrolic isomer **32** was obtained via a different synthetic pathway. Compound **46** bearing an azaindole unit and a pyrrole ring was successfully synthesized in three steps from 3-picoline and 2-cyanopyrrole.[23]

2.1.1. Synthesis of compounds 20–29 and 32 possessing a pyrrole instead of an imidazole heterocycle. Indole and 5-substituted indoles (Scheme 1) were selectively brominated in 3-position using bromine in DMF according to a known procedure.[24] Coupling of the 3-bromoindoles with pyrrole was carried out in dichloromethane and trifluoroacetic acid as described by Bocchi and Palla for unsubstituted 3-bromoindole.[25] It must be noticed that, with 3-bromoindoles bearing electron withdrawing groups, such as 5-nitro-3-bromoindole **2**, the corresponding 2,2′-indolylpyrrole was not formed, unchanged **2** was recovered together with small amounts of the dimer 2,2′-bis(5-nitroindole). Attempts to obtain compound **20** via a Diels–Alder reaction followed by oxidation of the cycloadduct failed. In a [4 + 2] cycloaddition approach to indolo[2,3-*a*]carbazoles, Barry et al.[26] did not observe the formation of the cycloadduct by heating 2,2′-bisindole with various dienophiles in acetonitrile. The reaction led to the Michaël adduct in low yields together with small amounts of the fully aromatized indolocarbazole. Diels–Alder assays performed by Desarbre and Bergman[27] with 3,3′-bisindoles and maleimides by heating in Ph_2O or in acetic acid gave directly the fully aromatized indolo[2,3-*a*]carbazoles. In



Scheme 1. Reagents and conditions: (a) Br_2 (l equiv), DMF, rt or 0 °C, 12 h (61–92% yield); (b) pyrrole (1 equiv), TFA, CH_2Cl_2 (67–72% yield); (c) maleimide or *N*-methylmaleimide (2 equiv), $SnCl_2$ catalytic, toluene, reflux (46–96% yield); (d) Pd black, nitrobenzene, 200 °C, 4–8 h (16–92%); (e) Pd/C, EtOAc/MeOH 1:2, H_2 1 bar 12–24 h (89–100%).

acetic acid, the reaction of indolylpyrrole **6** (R_1 = H) with maleimide only led to degradation of **6**. In all the experimental conditions tried, reaction of indolylpyrroles **6**–**9** with maleimide or *N*-methyl-maleimide never afforded the [4 + 2] cycloadducts, but using catalytic amounts of $SnCl_2$ in toluene, the Michaël adducts **10**–**17** were obtained in good yields (46–96%). For the final cyclization, several catalysts, solvents, temperatures, and work-up were tried.[16] The optimal yields were obtained with Pd black in nitrobenzene at 200 °C, the solvent was eliminated by filtration over silica gel.

Compound **32** (Scheme 2) was synthesized from **A**,[28] a known intermediate in the synthesis of indolocarbazoles. Reaction of **A** with pyrrolylmagnesium bromide in THF led to **30** in 78% yield. Compound **30** was irradiated in acetonitrile with a halogen lamp according to the method described by Terpin et al.[29] for the synthesis of didemnimide C, an alkaloid isolated from a caribbean ascidian, affording **32** in 87% yield. Removal of the Boc protective group using formic acid gave **32** in 76% yield.

2.1.2. Synthesis of azaisogranulatimide analogues 38, 39, 44, 45. Aza-isogranulatimide analogues **38**, **39** were synthesized from compound **33**, a precursor for the synthesis of aza-rebeccamycin analogues (Scheme 3).[30–32] Reaction of **33** with imidazolylmagnesium bromide in THF led to **34** in 90% yield. After protection of the azaindole NH with a Boc group, the cyclization was performed by irradiation in acetonitrile with a halogen lamp (500 W) to give **36** and **37** in similar yields (32% and 37%, respectively). Oxidation using MnO_2 in dichloromethane at room temperature for 12 h followed by removal of the Boc protective group with formic acid afforded compounds **38** and **39** in 77% and 47%, respectively.

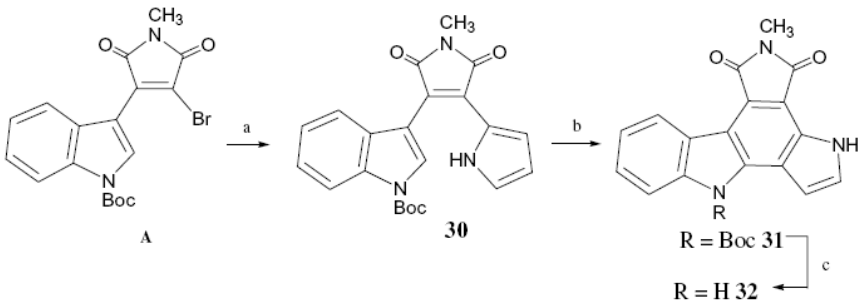
The identification of isomers **38** and **39** has been achieved by a NOE 1D experiment on the Boc protected intermediate **36**. In the ^{1}H NMR spectra of the intermediates **36** and **37** (Fig. 3), the signals of both imidazolic protons are singlets as observed in most of the compounds in this series. Due to the absence of coupling, the assignment of the structures was not simple.

A NOE 1D experiment has been performed with compound **36**. Selective irradiations of imidazolic protons at 7.23 and 7.64 ppm have been carried out. The irradiation of the proton shifted at 7.23 ppm induced an important overhauser effect (7%) on the proton (singlet) at 7.64 ppm. The irradiation of the proton shifted at 7.64 ppm induced an overhauser effect on the proton (singlet) at 7.23 ppm (11%) and on the proton (doublet) at 5.87 ppm (6%) (Fig. 4). Such effects can only be observed in compound **36** in which the two imidazolic protons are born by two vicinal carbons.

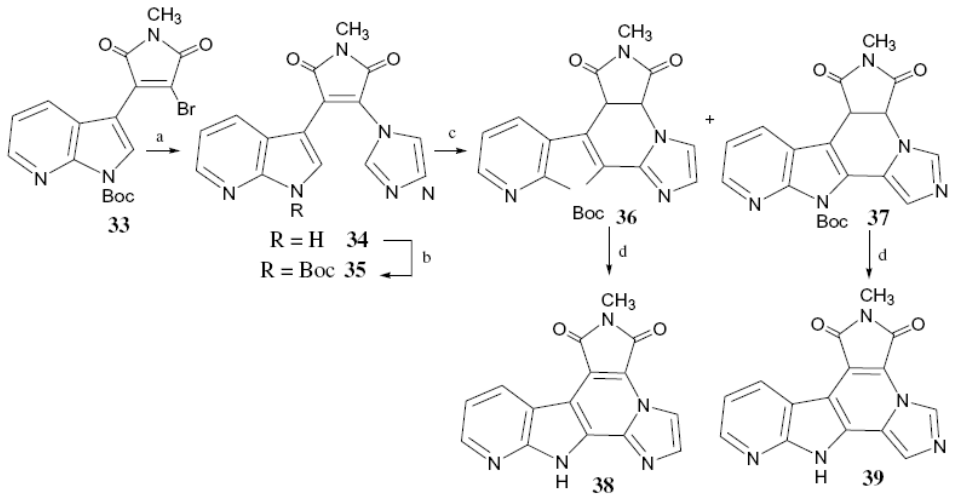
To synthesize isogranulatimide analogues bearing a sugar moiety (Scheme 4), a Mitsunobu reaction between compound **34** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose prepared in three steps from 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose[33] yielded compound **40** as the major product of the reaction (65% yield). A minor compound **40a** with the sugar part attached to the nitrogen of pyridine was isolated in 24% yield. In ^{1}H NMR spectra of both **40** and **40a**, an axial–axial coupling constant of 8.9 Hz between protons $H_{1'}$ and $H_{2'}$ is consistent with a β-*N*-glycosidic bond. The structures of **40** and **40a** were assigned from INEPTDN 1D NMR experiments allowing the observation of long range coupling ^{1}H—^{13}C (Fig. 5). From SDBS data[34] for 7-azaindole, it is possible to conclude that C_{7a}, in compound **40**, the most deshielded azaindolic carbon, corresponds to the signal at 147.8 ppm and C_2 to the signal at 130.1 ppm. The singlet at 8.18 ppm,which corresponds to the azaindolic H_2 proton, is coupled with the anomeric carbon (80.3 ppm, ^3J) and with a quaternary carbon at 147.8 ppm (^3J). The anomeric proton (doublet at 6.26 ppm) is coupled with a tertiary carbon at 130.1 ppm (azaindolic C_2) (^3J) and with a quaternary carbon at 147.8 ppm (^3J). It could be concluded that the sugar residue is attached to the nitrogen of the five-membered ring.

In compound **40a**, the doublet at 8.00 ppm is coupled with the anomeric carbon at 84.0 ppm and with the quaternary carbon at 151.0 ppm (azaindolic C_{7a}). $H_{1'}$ (doublet at 6.99 ppm, J = 8.9 Hz) shows a long range coupling with the quaternary carbon at 151.0 ppm and a tertiary carbon at 127.0 ppm (azaindolic C_6). Therefore, in **40a**, the carbohydrate residue is attached to the nitrogen of the six-membered ring.

Photocyclization of compound **40** was achieved with a halogen lamp in the conditions described above for **35**



Scheme 2. Reagents and conditions: (a) pyrrolyl-MgBr (3 equiv), THF, rt, 24 h (78% yield); (b) halogen lamp (500 W), CH_3CN, rt, 31 h (87% yield); (c) HCOOH, rt, 16 h (76% yield).



Scheme 3. Reagents and conditions: (a) EtMgBr, THF, imidazole (2.7 equiv), 50 °C, 5 h (90% yield); (b) $(Boc)_2O$, DMAP, THF, rt, 2 h (60% yield); (c) halogen lamp (500 W), CH_3CN, rt, 6.5 h (yields: **36**, 32%; **37**, 37%); (d) MnO_2, (6 equiv), CH_2Cl_2, rt, 12 h, then HCOOH, rt, 12 h (yields: **38**, 77%; **39**, 47%).

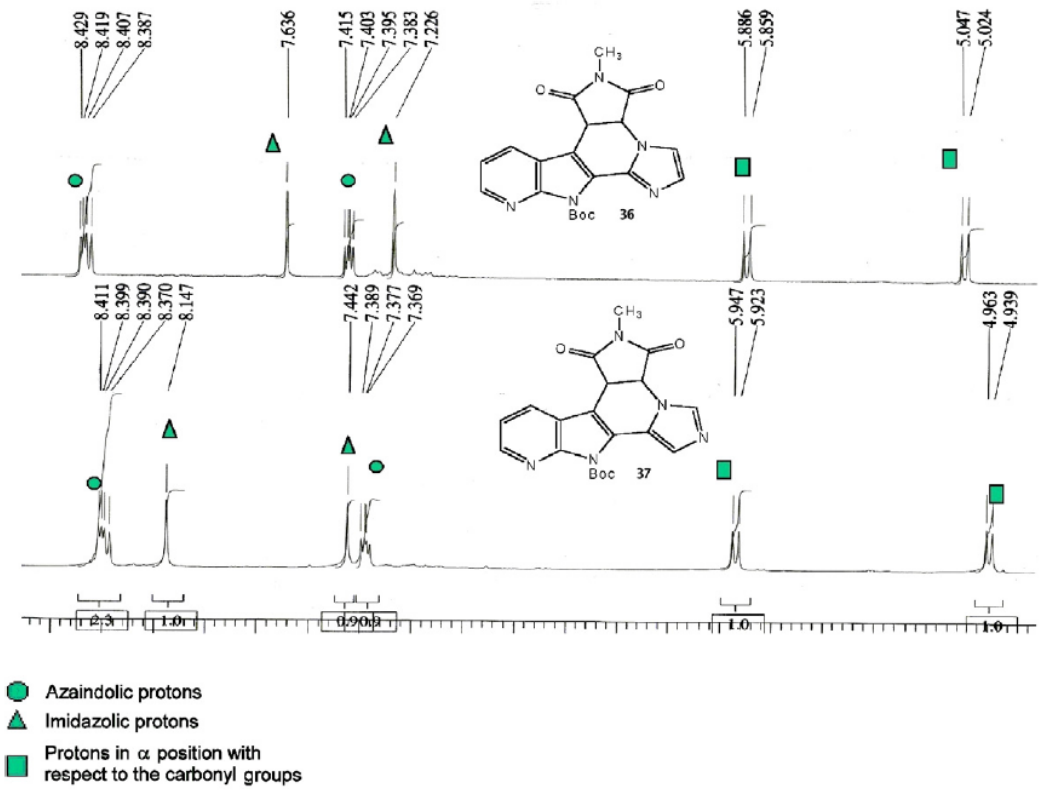


Figure 3. Comparison of ^1H NMR spectra of **36** and **37** in DMSO-d_6.

affording three compounds **41**, **42**, and **43** in 5%, 50%, and 18%, respectively. Oxidation of **42** and **43** with MnO_2 gave **41** and **43a** in 80% and 61% yields, respectively. The final removal of the protective groups on the sugar part was performed with 1 N MeONa in methanol to yield **44** and **45** (50% and 42% yields, respectively).

The ^1H NMR spectrum of compound **41** shows a mixture of conformers (ratio: 1:1). That was not observed in the deacetylated compound **44**. The structures of **44** and **45** could be assigned by comparison of their ^1H NMR spectra with those of the corresponding aglycones **38** and **39**. The signals of the aromatic protons show identical sequences.

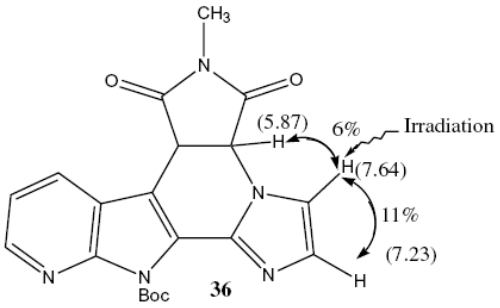
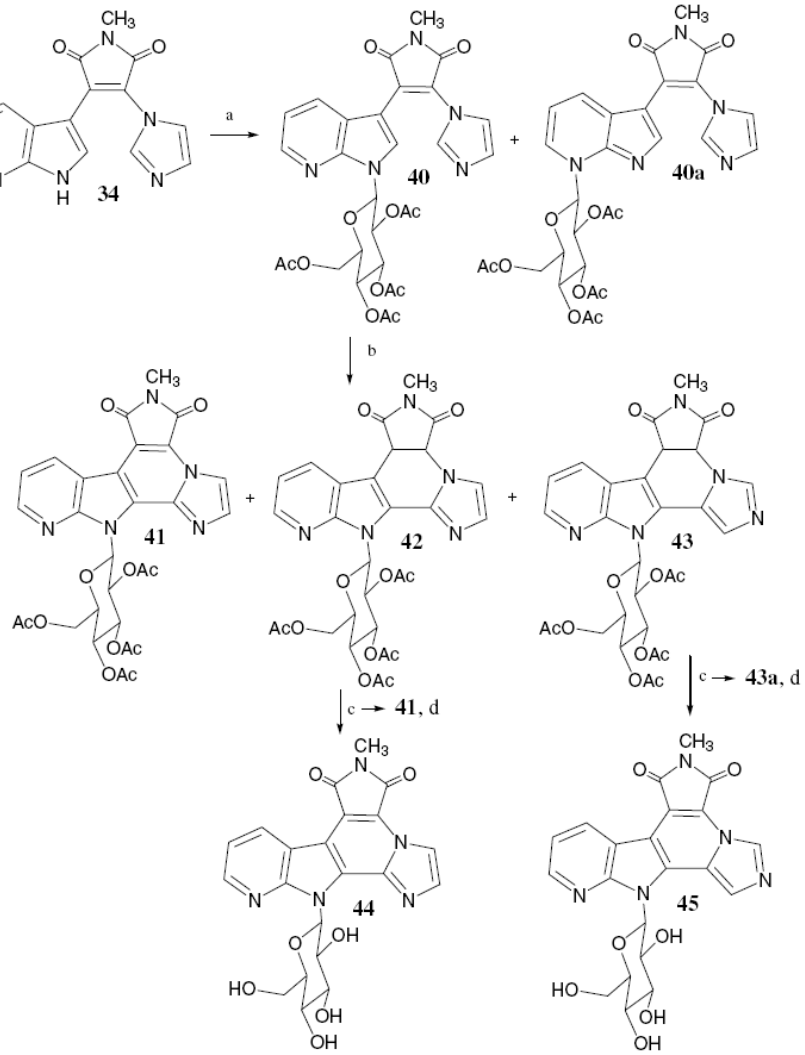


Figure 4. NOE 1D experiment on compound **36** (chemical shifts in ppm).

2.2. Chk1 inhibition

The percentages of Chk1 inhibition at a drug concentration of 10 μM were evaluated. For the most efficient compounds, the IC_{50} values were determined (Table 1). Compared with granulatimide, which was a stronger Chk1 inhibitor than isogranulatimide, compounds **24** and **26**, bearing either a bromine atom or a chlorine atom at the 5-position of the indole moiety, inhibit Chk1 with similar IC_{50} values. Compounds **20**, unsubstituted on the indole unit, and **28**, substituted in the 5-position with a hydroxy group, are the strongest Chk1 inhibitors in this series, they are more efficient than granulatimide. Based on the IC_{50} values, the following sequence of efficiency against Chk1 can be observed: **20**, **28** > **granulatimide**, **26**, **24** > **isogranulatimide** > **22** > **46**. Compounds **23**, **27**, **32**, **38**, **39**, **44**, and **45** proved to be poor Chk1 inhibitors. The presence of a methyl group on the imide nitrogen induces a strong decrease of Chk1 inhibition. These results are not surprising since, in the crystal structures of inhibitors such as staurosporine, UCN-01, SB218078, and isogranulati-



Scheme 4. Reagents and conditions: (a) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose, PPh_3, DEAD, −78 °C to rt then rt 15 h (yields: **40**, 65%; **40a** 24%); (b) halogen lamp (500 W), CH_3CN, rt, 6 h (yields: **41**, 5%; **42**, 50%, **43**, 18%); (c) MnO_2 (6 equiv), CH_2Cl_2, rt, 48 h (yields: **41**, 80%; **43a**, 61%); (d) MeONa/MeOH, rt, 12 h (yields: **44**, 50%; **45**, 42%).

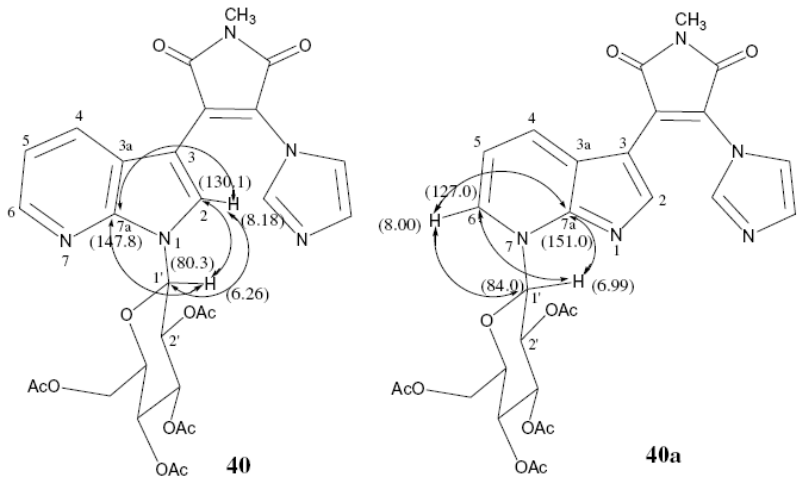


Figure 5. ^{1}H–^{13}C long range coupling in compounds **40** and **40a**.

Table 1. Percentages of Chk1 inhibition at a drug concentration of 10 μM

Compound	% of Chk1 inhibition at 10 μM	IC_{50} Chk1	L1210	DU145	A549	HT29
Granulatimide	93.9	0.08	2.8	2.8	11.4	5.7
Isogranulatimide	89.7	0.44	10	13.1	18.1	13.7
20	85.0	0.024	3.1	1.4	2.0	3.3
21	nd	nd	33	1.2	>100	>100
22	54.8	0.64	27	nd	23.2	13.7
23	10.3	nd	42.7	22.7	20	35.9
24	95.4	0.089	14.7	27.4	28.9	30.4
25	55.6	nd	41.2	nd	68.3	63.2
26	87.9	0.066	12.5	21.7	20.9	29
27	7.1	nd	48.7	>100	67	88.3
28	95.8	0.016	4.5	15.1	16.1	27.8
29	54.1	nd	5.4	nd	8.8	26.5
32	43.1	nd	4.9	1.9	47.1	5.9
38	36.1	nd	43.5	7.4	35.6	30.6
39	11.6	nd	8.8	13.5	7.4	9.7
44	10.7	nd	>100	64.8	128	53
45	15.1	nd	>100	56.1	78.5	52.5
46	76.6	3.6	29.2	4.6	19.7	17.1

IC_{50} values (μM) toward Chk1. In vitro antiproliferative activities against four tumor cell lines: murine leukemia L1210, and human DU145 prostate carcinoma, A549 non-small cell lung carcinoma, and HT29 colon carcinoma (IC_{50} (μM)).

mide in complex with Chk1, hydrogen bonds are observed between the lactam or the imide NH and the carbonyl of the Glu[85] residue in the ATP-binding site of the enzyme.[9,13] That is probably why aza compounds **38**, **39**, **44** and **45** as well as compound **32** bearing a N-methylated imide function are poor Chk1 inhibitors. The supplementary nitrogen atom in the azaindole analogues seems to be detrimental to the interaction with the ATP-binding site (compare compounds **20** and **46**). Concerning substitutions in the 5-position of the indole moiety, the following sequence of efficiency is observed: OH, H > Cl, Br > OBn. Moving the nitrogen atom in the pyrrole ring is detrimental to Chk1 inhibition (compare compounds **32** and **20**).

2.3. Inhibitory activities against various kinases

The kinase selectivity was evaluated with compounds **24** and **26**. Their inhibitory activities were tested against 14 kinases Chk1, AMPK, CAMKII, CKI, FGFR3, GSK3, LCK, MAPK1, MAPKAPK2, P70S6K, PKA, PKCβ, PKCα, PKCε. The percentages of activity at a drug concentration of 1 μM are reported in Table 2. In both cases, the strongest inhibition was found toward Chk1. The inhibitory activities of the most potent Chk1 inhibitors **20**, **24**, **26**, **28** toward Src tyrosine kinase were also determined (Table 3). These potent Chk1 inhibitors failed to inhibit Src significantly.

2.4. Interaction with DNA and topoisomerase I inhibition

Identical molecular studies as previously performed with rebeccamycins[35] were carried out with compounds **20**, **21**, **23**–**25**, **32**, **38**, and **44**, to investigate the capacity of the isogranulatimide analogues to bind to DNA and/or to inhibit topoisomerase I. No stabilization of the duplex structure of DNA was detected in the melting temperature studies. The absorption measurements also

Table 2. Percentages of inhibition of various kinases in the presence of compounds **24** and **26** at a concentration of 1 μM

Compound	Chk1	AMPK	CAMKII	CDK2/cyclin A	CKI	FGFR3	GSK3	LCK
24	6	29	40	69	94	32	39	92
26	14	46	55	88	104	50	44	91
	MAPK1	MAPKAPK2	P70S6K	PKA	PKCβ	PKCα	PKCε	
24	98	75	51	98	79	75	86	
26	88	99	26	103	98	85	90	

Checkpoint 1 kinase (Chk1), AMP-activated protein kinase (AMPK), Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII), casein kinase I (CKI), fibroblast growth factor receptor 3 (FGFR3), glycogen synthase kinase 3 (GSK3), lymphocyte-specific protein tyrosine kinase (LCK), MAP kinase 1 (MAPK1), mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2), kinase responsible for site specific phosphorylation of BAD (P70S6K), protein kinase A (PKA), protein kinases C β, α, ε isoforms (PKCβ, PKCα, PKCε).

Table 3. Percentages of Src kinase inhibition in the presence of drugs **20**, **24**, **26** and **28** at a concentration of 1 μM

Compound	% of Src inhibition at a drug concentration of 1 μM
20	32.5
24	22.1
26	22.3
28	1.2

showed no significant interaction with DNA and this was independently confirmed by DNase I footprinting and gel retardation experiments. In parallel, the DNA relaxation and cleavage assays showed no inhibition of topoisomerase I. Glycosylated indolocarbazoles such as rebeccamycin and its dechlorinated analogue were found to stabilize topoisomerase I–DNA complexes so as to stimulate the formation of DNA single strand breaks. In marked contrast, the isogranulatimide analogues tested here, bearing or not the sugar residue, were inactive in the same assays and did not function as topoisomerase I poisons, even when tested at a high concentration (50 μM).

2.5. Cytotoxicity

The in vitro cytotoxicities of the newly synthesized compounds as well as granulatimide and isogranulatimide were evaluated toward four tumor cell lines: murine leukemia L1210, and human DU145 prostate carcinoma, A549 non-small cell lung carcinoma, and HT29 colon carcinoma. The results are reported in Table 1 as the concentrations required to reduce cell growth by 50% (IC_{50}). It can be noticed that granulatimide and especially isogranulatimide do not exhibit strong cytotoxicities toward the cell lines tested. Compared with isogranulatimide, compounds **20**, **22**, **24**, **26**, **28** and compound **32** bearing a pyrrole instead of an imidazole unit and a free maleimide NH exhibit cytotoxicities in the same range. Generally, compounds possessing a *N*-methyl maleimide are less cytotoxic except compound **21** toward DU145 cells and compound **29** toward L1210 and A549 cells. It could be possible that a slight inhibition of cyclin-dependent kinases involved in the progression of the cell cycle is responsible for their weak cytotoxicities. An efficient inhibition of CDK2, a cyclin-dependant kinase, requires the presence of CO—NH function in the maleimide or lactam heterocycle of indolocarbazole compounds such as staurosporine and UCN-01.[36] Both CO and NH establish hydrogen bonds in the ATP-binding site of CDK2. That could explain why *N*-methyl compounds in our new series are less efficient in terms of cytotoxicity. Compared with isogranulatimide, the introduction of a 7-azaindole moiety instead of the indole unit (compounds **39** and **38**) does not change significantly the cytotoxicity. However, compound **46** is significantly less cytotoxic than compound **20**. Compared with the parent compounds **38** and **39**, the sugar unit of compounds **44** and **45** decreases the cytotoxicity.

3. Conclusion

General methods have been developed to synthesize isogranulatimide analogues in which either the imidazole has been replaced by a pyrrole and/or the indole moiety has been changed to a 7-azaindole unit. Moreover a glucose part has been attached to the 7-azaindole unit. The Chk1 inhibitory properties of these new granulatimide analogues have been determined. Some of them exhibit stronger Chk1 inhibitory activities than granulatimide and isogranulatimide. Moreover, the inhibitory activities of two compounds **24** and **26** evaluated toward a large panel of kinases showed a significant selectivity for Chk1. There is no correlation between Chk1 inhibitory activities and cytotoxicities, which is not surprising since a checkpoint inhibitor alone is not expected to be cytotoxic. Its cytotoxicity must be effective in the presence of a DNA damaging agent. In contrast with UCN-01, the new compounds did not bind to DNA and in contrast with rebeccamycin, bearing a maleimide upper heterocycle, they did not alter the function of topoisomerase I. Studies on cytotoxicities in the presence of a DNA damaging agent have now to be determined.

As observed for granulatimide and isogranulatimide, the cytotoxicities of the new compounds toward the four tumor cell lines tested were moderate. Their cytotoxicity could be due to a weak inhibition of other kinases than Chk1, such as cyclin-dependent kinases or to their weak solubility preventing cell penetration.

The study described here represents a contribution to structure-activity relationships in granulatimide series and confirms that this framework is especially interesting for designing new potent Chk1 inhibitors.

4. Experimental

4.1. Chemistry

IR spectra were recorded on a Perkin-Elmer 881 spectrometer (ν in cm^{-1}). NMR spectra were performed on a Bruker AC 400 (^1H: 400 MHz, ^{13}C: 100 MHz) (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), doublet (d), triplet (t), pseudo-triplet (pt), doubled triplet (dt), multiplet (m), br s (broad signal), tertiary carbons (C tert), quaternary carbons (C quat). The signals were assigned from ^1H—^1H COSY and ^{13}C—^1H correlations. Mass spectra (FAB+) were determined on a high resolution Fisons Autospec-Q spectrometer at CESAMO (Talence, France). Chromatographic purifications were performed by flash silica gel Geduran SI 60 (Merck) 0.040–0.063 mm or Kieselgel 60 (Merck) 0.063–0.200 mm column chromatography. Purity evaluation was performed through analytical HPLC using a HP1090 liquid chromatograph.

4.1.1. 3-Bromo-5-benzyloxyindole (2). To a solution of commercial 5-benzyloxy-indole (893 mg, 4 mmol) in DMF (20 mmol) was added dropwise a solution of Br_2 (217 μL, 4 mmol) in DMF (20 mL). The light-protected mixture was stirred at room temperature for 12 h then poured into water and ice (200 mL) containing NH_4OH (1 mL) and saturated aqueous $Na_2S_2O_3$ (0.2 mL). After filtration, the residue was washed with water to give **2** (1.11 g, 3.67 mmol, 92% yield) as a pale gray solid. Mp 89–92 °C. IR (KBr) ν_{NH} 3420 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{15}H_{12}NOBr$ 301.0102, found 301.0097. ^1H NMR (400 MHz, DMSO-d_6): 5.17 (2H, s), 6.90–7.00 (2H, m), 7.37 (2H, d, J = 8.8 Hz), 7.44 (2H, t, J = 7.6 Hz), 7.53 (3H, m), 11.38 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 69.7 (CH_2), 88.3, 126.4, 130.5, 137.6, 153.1 (C quat arom), 100.7, 113.0, 113.3, 125.3, 127.6 (2C), 127.7, 128.4 (2C) (C tert arom).

4.1.2. 3-Bromo-5-chloroindole (3). Identical procedure as described for **2** afforded from 5-chloro-indole (606 mg, 4 mmol) compound **3** (592 mg, 2.57 mmol, 65% yield) as a brown solid. Mp 84 °C. IR (KBr) ν_{NH} 3420 cm^{-1}. HRMS (FAB+) (M^+) calcd for C_8H_5NClBr 228.9294, found 228.9295. ^1H NMR (400 MHz, DMSO-d_6): 7.22 (1H, dd, J_1 = 8.6 Hz, J_2 = 1.5 Hz), 7.43 (1H, s), 7.50 (1H, d, J = 8.7 Hz), 7.68 (1H, d, J = 2.4 Hz), 11.72 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 88.0, 124.6, 127.2, 133.9 (C quat arom), 113.8, 117.0, 122.3, 126.7 (C tert arom).

4.1.3. 3,5-Dibromoindole (4). Identical procedure as described for **2** afforded from 5-chloro-indole (784 mg, 4 mmol) compound **4** (638 mg, 2.45 mmol, 61% yield) as a dark brown solid. Mp 94 °C. IR (KBr) ν_{NH} 3420 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_8H_5NBr_2$ 272.8789, found 272.8796. ^1H NMR (400 MHz, DMSO-d_6): 7.33 (1H, d, J = 7.8 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.57 (1H, s), 7.66 (1H, s), 11.73 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 114.2, 120.0, 124.8, 126.5 (C tert arom), 87.8, 112.4, 127.9, 134.1 (C quat arom).

4.1.4. 3-Bromo-4-nitroindole (5). Identical procedure as described for **2** afforded from 5-nitro-indole (649 mg, 4 mmol) compound **5** (878 mg, 3.64 mmol, 91% yield) as a pale gray solid. Mp 191–194 °C. IR (KBr) ν_{NH} 3320 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 7.65 (1H, d, J = 9.0 Hz), 7.96 (1H, s), 8.10 (1H, d, J = 8.7 Hz), 8.38 (1H, s), 12.11 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 91.0, 125.6, 138.5, 141.3 (C quat arom), 112.9, 114.9, 117.4, 129.0 (C tert arom).

4.1.5. 5-Benzyloxy-2-(1*H*-pyrrol-2-yl)-1*H*-indole (7). To 3-bromo-5-benzyloxy-indole **2** (453 mg, 1.5 mmol) dissolved in CH_2Cl_2 (8 mL) was added a solution of pyrrole (101 mg, 1.5 mmol) in CH_2Cl_2 (7 mL) then trifluoroacetic acid (45 μL). The mixture was stirred at room temperature for 4 h. NH_4OH was added until basic pH and the solution was evaporated to dryness. The residue was purified by flash chromatography (eluent: EtOAc/cyclohexane 2:8) to give **7** (298 mg, 1.03 mmol, 69% yield) as a pale green solid. Mp 178–182 °C. IR (KBr) ν_{NH} 3380–3420 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{19}H_{17}N_2O$ 289.1341, found 289.1336. ^1H NMR (400 MHz, DMSO-d_6): 5.12 (2H, s), 6.15 (1H, m), 6.55 (2H, m), 6.76 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz), 6.88 (1H, m), 7.09 (1H, d, J = 2.3 Hz), 7.23 (1H, d, J = 8.7 Hz), 7.36 (1H, m), 7.44 (2H, t, J = 7.7 Hz), 7.52 (2H, d, J = 7.1 Hz), 11.01 (1H, s, NH), 11.32 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 69.7 (CH_2), 95.1, 102.9, 105.4, 108.6, 110.9, 111.1, 118.9, 127.5 (3C), 128.3 (2C) (C tert arom), 125.0, 129.2, 131.5, 133.2, 137.9, 152.5 (C quat arom).

4.1.6. 5-Chloro-2-(1*H*-pyrrol-2-yl)-1*H*-indole (8). Identical procedure as described for **7** gave from 3-chloro-5-bromo-indole **3** (461 mg, 2 mmol) compound **8** (313 mg, 1.44 mmol, 72% yield) as a pale green solid. Mp 223–227 °C. IR (KBr) ν_{NH} 3400, 3420 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{12}H_{10}N_2Cl$ 217.0533, found 217.0534. ^1H NMR (400 MHz, DMSO-d_6): 6.17 (1H, m), 6.62 (2H, br s), 6.92 (1H, m), 7.03 (1H, dd, J_1 = 8.3 Hz, J_2 = 1.6 Hz), 7.34 (1H, d, J = 8.5 Hz), 7.52 (1H, d, J = 1.5 Hz), 11.42 (2H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 94.7, 106.2, 108.8, 111.9, 118.3, 119.6, 120.2 (C tert arom), 123.5, 124.4, 130.0, 134.2, 134.7 (C quat arom).

4.1.7. 5-Bromo-2-(1*H*-pyrrol-2-yl)-1*H*-indole (9). Identical procedure as described for **7** gave from 3,5-bromo-indole **3** (260 mg, 1 mmol) compound **9** (175 mg, 0.67 mmol, 67% yield) as a white solid. Mp 245 °C. IR (KBr) ν_{NH} 3400, 3410 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{12}H_9N_2Br$ 259.9949, found 259.9952. ^1H NMR (400 MHz, DMSO-d_6): 6.17 (1H, m), 6.62 (2H, m), 6.92 (1H, m), 7.14 (1H, dd, J_1 = 8.1 Hz, J_2 = 1.6 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 1.5 Hz), 11.41 (2H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 94.6, 106.2, 108.8, 112.4, 119.7, 121.3, 122.8 (C tert arom), 111.5, 124.4, 130.8, 134.1, 135.0 (C quat arom).

4.1.8. 3-[2-(1*H*-Pyrrol-2-yl)-1*H*-indol-3-yl]-2,5-pyrrolidinedione (10). A mixture of 2,2′-indolylpyrrole **6** (50 mg, 0.274 mmol), maleimide (53 mg, 0.548 mmol), and catalytic amounts of $SnCl_2$ in toluene (15 mL) was

refluxed for 24 h. After evaporation of toluene, the residue was purified by flash chromatography (eluent: EtOAc/cyclohexane 3:7) to give **10** (69 mg, 0.247 mmol, 90% yield) as a light green solid. Physical and spectral data are given in Ref. 16.

4.1.9. 1-Methyl-3-[2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-2,5-pyrrolidinedione (11). Identical procedure as described for **10** gave from 2,2′-indolylpyrrole **6** (100 mg, 0.548 mmol) and *N*-methylmaleimide (122 mg, 1.10 mmol) compound **11** (144 mg, 0.491 mmol, 89% yield) as a pale yellow solid. Mp 142 °C. IR (KBr) $\nu_{C=O}$ 1740, 1770 cm^{-1}, ν_{NH} 3200–3400 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{17}H_{16}N_3O_2$ 294.1243, found 294.1232. ^1H (400 MHz, DMSO-d_6): 2.82 (1H, dd, J_1 = 18.1 Hz, J_2 = 5.2 Hz), 3.04 (3H, s, NCH_3), 3.35 (1H, dd, J_1 = 18.1 Hz, J_2 = 9.7 Hz), 4.59 (1H, dd, J_1 = 9.6 Hz, J_2 = 5.2 Hz), 6.26 (1H, m), 6.47 (1H, m), 7.03 (2H, m), 7.11 (1H, d, J = 7.3 Hz), 7.13 (1H, t, J = 7.2 Hz), 7.42 (1H, d, J = 8.0 Hz), 11.20 (2H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 24.7 (CH_3), 36.0 (CH_2), 37.6 (CH), 106.0, 122.8, 126.1, 130.7, 135.8 (C quat arom), 108.7, 108.9, 111.4, 117.5, 119.3, 119.7, 121.3 (C tert arom), 176.8, 178.8 (C=O).

4.1.10. 3-[5-Benzyloxy-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-2,5-pyrrolidinedione (12). Identical procedure as described for **10** gave from **7** (288 mg, 1 mmol) and maleimide (194 mg, 2 mmol) compound **12** (263 mg, 0.68 mmol, 68% yield) as a pale yellow solid. Mp 103–107 °C. IR (KBr) $\nu_{C=O}$ 1690, 1740 cm^{-1}, ν_{NH} 3250–3440 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{23}H_{20}N_3O_3$ 386.1505, found 386.1486. ^1H NMR (400 MHz, DMSO-d_6): 2.75 (1H, dd, J_1 = 18.1 Hz, J_2 = 5.5 Hz), 3.26 (1H, dd, J_1 = 18.0 Hz, J_2 = 9.8 Hz), 4.54 (1H, dd, J_1 = 9.8 Hz, J_2 = 5.5 Hz), 5.08 (2H, s), 6.24 (1H, m), 6.45 (1H, br s), 6.77 (1H, br s), 6.88 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz), 7.00 (1H, br s), 7.31 (1H, d, J = 8.7 Hz), 7.37 (1H, t, J = 7.2 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.49 (2H, d, J = 7.3 Hz), 10.99 (1H, s, NH), 11.11 (1H, s, NH), 11.49 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 37.0 (CH_2), 38.9 (CH), 69.9 (CH_2O), 101.9, 108.5, 108.9, 111.2, 112.0, 119.6, 127.7, 127.8 (2C), 128.4 (2C) (C tert arom), 105.7, 122.9, 126.6, 131.1, 131.4, 137.5, 152.2 (C quat arom), 178.1, 180.2 (C=O).

4.1.11. 3-[5-Benzyloxy-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-1-methyl-2,5-pyrrolidinedione (13). Identical procedure as described for **11** gave from **7** (148 mg, 0.513 mmol) and *N*-methylmaleimide (114 mg, 1.03 mmol) compound **13** (167 mg, 0.418 mmol, 82% yield) as a pale yellow solid. Mp 89–94 °C. IR (KBr) $\nu_{C=O}$ 1680–1700 cm^{-1}, ν_{NH} 3300–3420 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{24}H_{22}N_3O_3$ 400.1661, found 400.1654. ^1H NMR (400 MHz, DMSO-d_6): 2.74 (1H, dd, J_1 = 18.0 Hz, J_2 = 5.3 Hz), 2.97 (3H, s, CH_3), 3.28 (1H, dd, J_1 = 18.1 Hz, J_2 = 9.6 Hz), 4.51 (1H, dd, J_1 = 9.5 Hz, J_2 = 5.4 Hz), 5.07 (2H, s), 6.22 (1H, m), 6.39 (1H, m), 6.59 (1H, d, J = 2.1 Hz), 6.85 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz), 6.99 (1H, m), 7.29 (1H, d, J = 8.7 Hz), 7.35 (1H, m), 7.39–7.48 (4H, m), 11.00 (1H, s, NH), 11.12 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 24.6 (CH_3), 35.6 (CH_2), 37.5 (CH), 69.8 (CH_2O), 101.5, 108.5, 108.8, 111.5, 112.0, 119.6, 127.5, 127.6 (2C), 128.3 (2C) (C tert arom), 105.7, 122.8, 126.4, 131.0, 131.4, 137.6, 152.2 (C quat arom), 176.6, 178.6 (C=O).

4.1.12. 3-[5-Chloro-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-2,5-pyrrolidinedione (14). Identical procedure as described for **10** gave from **8** (130 mg, 0.600 mmol) and maleimide (117 mg, 1.200 mmol) compound **14** (104 mg, 0.331 mmol, 56% yield) as a pale yellow solid. Mp 138–144 °C. IR (KBr) $\nu_{C=O}$ 1700, 1780 cm^{-1}, ν_{NH} 3100–3500 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_{12}N_3O_2Cl$ 313.0618, found 313.0629. ^1H NMR (400 MHz, DMSO-d_6): 2.75 (1H, dd, J_1 = 18.2 Hz, J_2 = 5.6 Hz), 3.27 (1H, dd, J_1 = 18.2 Hz, J_2 = 9.8 Hz), 4.54 (1H, dd, J_1 = 9.7 Hz, J_2 = 5.6 Hz), 6.25 (1H, m), 6.46 (1H, br s), 7.03 (1H, m), 7.13 (1H, dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 7.16 (1H, br s), 7.40 (1H, d, J = 8.4 Hz), 11.20 (1H, s, NH), 11.37 (1H, s, NH), 11.52 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 37.1 (CH_2), 38.7 (CH), 105.8, 122.3, 123.6, 127.4, 132.3, 134.3 (C tert arom), 109.0, 109.1, 112.9, 116.6, 120.1, 121.1 (C quat arom), 178.0, 179.9 (C=O).

4.1.13. 3-[5-Chloro-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-1-methyl-2,5-pyrrolidinedione (15). Identical procedure as described for **11** gave from **8** (130 mg, 0.600 mmol) and de *N*-methylmaleimide (133 mg, 1.200 mmol) compound **15** (156 mg, 0.476 mmol, 79% yield). Mp 92–102 °C. IR (KBr) $\nu_{C=O}$ 1690, 1770 cm^{-1}, ν_{NH} 3200–3500 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{17}H_{14}N_3O_2Cl$ 327.0775, found 327.0779. ^1H NMR (400 MHz, DMSO-d_6): 2.80 (1H, dd, J_1 = 18.1 Hz, J_2 = 5.6 Hz), 3.00 (3H, s, CH_3), 3.31 (1H, dd, J_1 = 18.0 Hz, J_2 = 9.5 Hz), 4.56 (1H, dd, J_1 = 9.5 Hz, J_2 = 5.6 Hz), 6.24 (1H, m), 6.43 (1H, m), 7.02 (1H, m), 7.12 (1H, dd, J_1 = 7.2 Hz, J_2 = 2.1 Hz), 7.13 (1H, s), 7.41 (1H, d, J = 9.0 Hz), 11.21 (1H, s, NH), 11.39 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 24.7 (CH_3), 35.8 (CH_2), 37.3 (CH), 105.7, 122.1, 123.7, 127.4, 132.4, 134.2 (C tert arom), 109.0, 109.1, 112.8, 116.7, 120.1, 121.2 (C quat arom), 176.5, 178.4 (C=O).

4.1.14. 3-[5-Bromo-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-2,5-pyrrolidinedione (16). Identical procedure as described for **10** gave from **9** (100 mg, 0.383 mmol) and maleimide (74 mg, 0.766 mmol) compound **16** (63 mg, 0.279 mmol, 46% yield) as a pale green solid. Mp 163 °C. IR (KBr) $\nu_{C=O}$ 1720–1780 cm^{-1}, ν_{NH} 3260–3420 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_{12}N_3O_2Br$ 357.0113, found 357.0118. ^1H NMR (400 MHz, DMSO-d_6): 2.75 (1H, dd, J_1 = 18.1 Hz, J_2 = 5.6 Hz), 3.28 (1H, dd, J_1 = 18.1 Hz, J_2 = 9.9 Hz), 4.54 (1H, dd, J_1 = 9.8 Hz, J_2 = 5.6 Hz), 6.25 (1H, m), 6.47 (1H, br s), 7.03 (1H, m), 7.24 (1H, dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz), 7.32 (1H, s), 7.37 (1H, d, J = 8.5 Hz), 11.19 (1H, s, NH), 11.37 (1H, s, NH), 11.51 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 37.2 (CH_2), 38.7 (CH), 105.6, 111.6, 122.2, 128.1, 132.1, 134.5 (C quat arom), 109.0, 109.1, 113.3, 119.6, 120.1, 123.6 (C tert arom), 178.0, 179.9 (C=O).

4.1.15. 3-[5-Bromo-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-1-methyl-2,5-pyrrolidinedione (17). Identical procedure as described for **11** gave from **9** (100 mg, 0.383 mmol) and *N*-methylmaleimide (85 mg, 0.766 mmol) compound **17** (137 mg, 0.369 mmol, 96% yield) as a pale green solid. Mp 81 °C. IR (KBr) $\nu_{C=O}$ 1750–1790 cm^{-1}, ν_{NH} 3340–3400 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{17}H_{14}N_3O_2Br$ 371.0269, found 371.0271. ^1H NMR (400 MHz, DMSO-d_6): 2.80 (1 H, dd, J_1 = 17.8 Hz, J_2 = 5.8 Hz), 3.29 (1H, dd, J_1 = 17.8 Hz, J_2 = 9.6 Hz), 3.38 (3H, s), 4.57 (1H, dd, J_1 = 9.5 Hz, J_2 = 5.4 Hz), 6.23 (1H, m), 6.42 (1H, br s), 7.02 (1H, m), 7.22 (1H, dd, J_1 = 6.9 Hz, J_2 = 1.6 Hz), 7.28 (1H, s), 7.36 (1H, d, J = 8.5 Hz), 11.21 (1H, s, NH), 11.40 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 24.7 (CH_3), 35.9 (CH_2), 37.4 (CH), 105.6, 111.7, 122.1, 128.1, 132.2, 134.5 (C quat arom), 109.0, 109.2, 113.3, 119.7, 120.1, 123.8 (C tert arom), 176.5, 178.5 (C=O).

4.1.16. 3-[5-Hydroxy-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-2,5-pyrrolidinedione (18). A suspension of compound **12** (100 mg, 0.259 mmol) and 10% Pd/C (15 mg) in EtOAc (5 mL) and methanol (10 mL) was hydrogenated (1 bar) for 12 h. 10% Pd/C (10 mg) was added and the mixture hydrogenated for 12 h more. After filtration over Celite, the solid residue was washed with EtOAc and methanol. The filtrate was evaporated to give **18** (76 mg, 0.259 mmol, 100% yield) as a light gray solid. Mp 178–180 °C. IR (KBr) $\nu_{C=O}$ 1700, 1720 cm^{-1}, $\nu_{NH,OH}$ 3000–3500 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_{13}N_3O_3$ 295.0957, found 295.0952. ^1H NMR (400 MHz, DMSO-d_6): 2.73 (1H, dd, J_1 = 18.2 Hz, J_2 = 5.4 Hz), 3.25 (1H, dd, J_1 = 18.1 Hz, J_2 = 9.7 Hz), 4.48 (1H, dd, J_1 = 9.7 Hz, J_2 = 5.4 Hz), 6.22 (1H, m), 6.41 (1H, br s), 6.54 (1H, d, J = 1.5 Hz), 6.63 (1H, dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz), 6.96 (1H, br s), 7.19 (1H, d, J = 8.5 Hz), 8.80 (1H, s, OH), 10.80 (1H, s, NH), 11.05 (1H, s, NH), 11.45 (1H, br s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 36.9 (CH_2), 38.9 (CH), 101.7, 108.2, 108.8, 111.3, 111.8, 119.4 (C tert arom), 105.2, 123.2, 126.8, 130.2, 130.9, 150.7 (C quat arom), 178.1, 180.3 (C=O).

4.1.17. 3-[5-Hydroxy-2-(1*H*-pyrrol-2-yl)-1*H*-indol-3-yl]-1-methyl-2,5-pyrrolidinedione (19). Identical method as described for **18** gave from **13** (100 mg, 0.250 mmol) compound **19** (69 mg, 0.223 mmol, 89% yield) as a pale gray solid. Mp 148–154 °C. IR (KBr) $\nu_{C=O}$ 1680, 1720 cm^{-1}, $\nu_{NH,OH}$ 3300–3400 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{17}H_{16}N_3O_3$ 310.1192, found 310.1183. ^1H NMR (400 MHz, DMSO-d_6): 2.73 (1H, dd, J_1 = 18.2 Hz, J_2 = 5.1 Hz), 3.02 (3H, s, CH_3), 3.31 (1H, dd, J_1 = 18.0 Hz, J_2 = 9.4 Hz), 4.48 (1H, dd, J_1 = 9.6 Hz, J_2 = 5.0 Hz), 6.21 (1H, m), 6.39 (2H, br s), 6.61 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz), 6.98 (1H, m), 7.18 (1H, d, J = 8.5 Hz), 8.74 (1H, s), 10.82 (1H, s, NH), 11.09 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 24.6 (CH_3), 35.8 (CH_2), 37.5 (CH), 101.6, 108.3, 108.8, 111.3, 111.8, 119.4 (C tert arom), 105.3, 123.1, 126.7, 130.2, 130.9, 150.7 (C quat arom), 176.7, 178.8 (C=O).

4.1.18. Pyrrolo[3′,4′:5,6]indolizino[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (20). A suspension of **10** (100 mg, 0.358 mmol) and Pd black (39 mg, 0.358 mmol) in nitrobenzene (5 mL) was refluxed for 8 h. After cooling to room temperature, cyclohexane (5 mL) was added and the mixture was filtered over a sintered glass containing silica gel. Nitrobenzene was eliminated by elution (eluent: from cyclohexane to cyclohexane/CH_2Cl_2 95:5). The product of the reaction was eluted with a mixture CH_2Cl_2/MeOH/TFA (10:1:0.05). After removal of the solvents, the residue was dissolved in EtOAc. The solution was washed successively with saturated aqueous $NaHCO_3$, water, and brine, then dried over $MgSO_4$. Evaporation to dryness afforded **20** (70.3 mg, 0.255 mmol, 72% yield) as a dark violet solid. Physical and spectral data are given in Ref. 16.

4.1.19. 2-Methyl-pyrrolo[3′,4′:5,6]indolizino[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (21). Identical procedure as for **20** gave from **11** (100 mg, 0.341 mmol) and Pd black (37 mg, 0.341 mmol) compound **21** (88 mg, 0.304 mmol, 89% yield) as a dark violet solid. Mp 226–228 °C. IR (KBr) $\nu_{C=O}$ 1700–1750 cm^{-1}, ν_{NH} 3400 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{17}H_{12}N_3O_2$ 290.0929, found 290.0933. ^1H NMR (400 MHz, DMSO-d_6): 3.01 (3H, s, CH_3), 7.04 (2H, m), 7.28 (1H, t, J = 7.6 Hz), 7.43 (1H, t, J = 8.0 Hz), 7.59 (1H, d, J = 8.1 Hz), 8.14 (1H, m), 8.44 (1H, d, J = 7.8 Hz), 12.55 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 99.7, 111.6, 116.0, 120.8 (2C), 122.2, 124.8 (C tert arom), 103.6, 116.1, 120.5, 121.4, 124.3, 133.5, 138.8 (C quat arom), 165.0, 167.9 (C=O).

4.1.20. 5-Benzyloxy-pyrrolo[3′,4′:5,6]indolizino[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (22). Identical procedure as for **20** was carried out from **12** (70 mg, 0.182 mmol) and Pd black (20 mg, 0.188 mmol). A final purification by flash chromatography (eluent: EtOAc/cyclohexane 3:7) afforded compound **22** (24 mg, 0.063 mmol, 35% yield) as a dark violet solid. Mp 275 °C. IR (KBr) $\nu_{C=O}$ 1710, 1720 cm^{-1}, ν_{NH} 3100–3500 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{23}H_{16}N_3O_3$ 382.1192, found 382.1191. ^1H NMR (400 MHz, DMSO-d_6): 5.24 (2H, s, CH_2), 7.10 (2H, m), 7.15 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.5 Hz), 7.38 (1H, m), 7.45 (2H, t, J = 7.2 Hz), 7.56 (1H, d, J = 8.9 Hz), 7.58 (2H, d, J = 7.2 Hz), 8.20 (1H, d, J = 2.4 Hz), 8.2 (1H, m), 11.07 (1H, s, NH), 12.54 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 69.8 (CH_2), 99.7, 106.3, 112.4, 114.5, 115.9, 127.8-128.4 (C tert arom), 103.7, 117.1, 120.8, 122.2, 124.5, 133.7, 134.2, 137.3, 153.4 (C quat arom), 166.4, 169.3 (C=O).

4.1.21. 5-Benzyloxy-2-methyl-pyrrolo[3′,4′:5,6]indolizino-[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (23). Identical procedure as described above for **20** gave from **13** (100 mg, 0.250 mmol) and Pd black (27 mg, 0.250 mmol) compound **23** (74 mg, 0.187 mmol, 75% yield) as a dark violet solid. Mp 120 °C. IR (KBr) $\nu_{C=O}$ 1680–1700 cm^{-1}, ν_{NH} 3200–3600 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{24}H_{18}N_3O_3$ 396.1348, found 396.1334. ^1H NMR (400 MHz, DMSO-d_6): 3.13 (3H, s, CH_3), 5.24 (2H, s, CH_2O), 7.06–7.12 (2H, m), 7.16 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz), 7.38 (1H, m), 7.46 (2H, t, J = 7.5 Hz), 7.55 (1H, d, J = 9.0 Hz), 7.58 (2H, d, J = 7.4 Hz), 8.21 (1H, d, J = 2.2 Hz), 8.25 (1H, d, J = 1.4 Hz), 12.56 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.5 (CH_3), 69.8 (CH_2), 99.8,

106.0, 112.5, 114.7, 116.0, 127.7–128.4 (C tert arom), 103.9, 116.2, 120.4, 122.1, 124.4, 133.8, 134.1, 137.3, 153.5 (C quat arom), 165.2, 167.9 (C=O).

4.1.22. 5-Chloro-pyrrolo[3′,4′:5,6]indolizino[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (24). Identical procedure as for **20** gave from **14** (86 mg, 0.274 mmol) and Pd black (30 mg, 0.274 mmol) compound **24** (44 mg, 0.142 mmol, 52% yield) as a dark violet solid. Mp 298–304 °C. IR (KBr) $\nu_{C=O}$ 1700, 1710 cm^{-1}, ν_{NH} 3100–3400 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{16}H_9N_3O_2Cl$ 310.0383, found 310.0377. ^1H NMR (400 MHz, DMSO-d_6): 7.13 (2H, s), 7.43 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz), 7.64 (1H, d, J = 8.6 Hz), 8.26 (1H, s), 8.50 (1H, s), 11.13 (1H, s, NH), 12.82 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 100.5, 113.3, 114.5, 116.2, 121.2, 124.5 (C tert arom), 102.9, 116.6, 121.8, 122.8, 124.2, 125.1, 134.4, 137.3 (C quat arom), 166.3, 169.3 (C=O).

4.1.23. 5-Chloro-2-methyl-pyrrolo[3′,4′:5,6]indolizino-[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (25). Identical procedure as for **20** gave from **15** (70 mg, 0.214 mmol) and Pd black (23 mg, 0.214 mmol) compound **25** (56 mg, 0.174 mmol, 81% yield) as a dark violet solid. Mp 249 °C. IR (KBr) $\nu_{C=O}$ 1690, 1710 cm^{-1}, ν_{NH} 3200–3600 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{17}H_{11}N_3O_2Cl$ 324.0540, found 324.0523. ^1H NMR (400 MHz, DMSO-d_6): 3.13 (3 H, s, CH_3), 7.15 (2H, s), 7.44 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.0 Hz), 7.67 (1H, d, J = 8.5 Hz), 8.28 (1H, br s), 8.52 (1H, br s), 12.87 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.3 (CH_3), 100.4, 113.1, 114.3, 116.1, 121.0, 124.4 (C tert arom), 102.7, 115.6, 122.5, 123.9, 125.0, 129.2, 134.1, 137.1 (C quat arom), 164.8, 167.7 (C=O).

4.1.24. 5-Bromo-pyrrolo[3′,4′:5,6]indolizino[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione 26. Identical procedure as for **20** gave from **16** (100 mg, 0.279 mmol) and Pd black (28 mg, 0.279 mmol) compound **26** (41 mg, 0.116 mmol, 42% yield) as a dark violet solid. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1720 cm^{-1}, ν_{NH} 3200–3440 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_8N_3O_2Br$ 352.9800, found 352.9801. ^1H NMR (400 MHz, DMSO-d_6): 7.13 (2H, m), 7.53 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.5 Hz), 7.60 (1H, d, J = 8.6 Hz), 8.27 (1H, br s), 8.65 (1H, d, J = 1.5 Hz), 11.15 (1H, s, NH), 12.86 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 100.6, 113.8, 114.5, 116.2, 124.2, 127.1 (C tert arom), 102.7, 112.9, 116.6, 121.8, 123.4, 134.2, 137.5 (C quat arom), 166.3, 169.3 (C=O).

4.1.25. 5-Bromo-2-methyl-pyrrolo[3′,4′:5,6]indolizino-[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (27). Identical procedure as for **20** gave from **17** (87 mg, 0.234 mmol) and Pd black (25 mg, 0.235 mmol) compound **27** (79 mg, 0.215 mmol, 92% yield) as a dark violet solid. Mp > 300 °C. IR (KBr): $\nu_{C=O}$ 1650, 1690 cm^{-1}, ν_{NH} 3300–3500 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{17}H_{10}N_3O_2Br$, 366.9956, found 366.9958. ^1H NMR (400 MHz, DMSO-d_6): 3.13 (3H, s, CH_3), 7.14 (2H, s), 7.56 (1H, dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz), 7.62 (1H, d, J = 8.7 Hz), 8.27 (1H, s), 8.67 (1H, s), 12.85 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.5 (CH_3), 100.6, 113.8, 114.4, 116.3, 124.1, 127.1 (C tert arom), 102.7, 113.0, 115.9, 121.4, 123.2, 134.1, 137.5 (C quat arom), 165.1, 168.0 (C=O).

4.1.26. 5-Hydroxy-pyrrolo[3′,4′:5,6]indolizino[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione 28. Identical procedure as for **20** gave from **18** (60 mg, 0.203 mmol) and Pd black (23 mg, 0.274 mmol) compound **28** (9.4 mg, 0.032 mmol, 16% yield) as a dark red solid. Mp >275 °C. IR (KBr) $\nu_{C=O}$ 1710, 1740 cm^{-1}, $\nu_{NH,OH}$ 3000–3300 cm^{-1}. HRMS (FAB+) (M^+) calcd for $C_{16}H_9N_3O_3$ 291.0644, found 291.0636. ^1H NMR (400 MHz, DMSO-d_6): 6.92 (1 H, dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz), 7.07 (2H, m), 7.44 (1H, d, J = 8.6 Hz), 7.99 (1H, d, J = 2.2 Hz), 8.24 (1H, t, J = 2.3 Hz), 9.22 (1H, s, OH), 11.01 (1H, s, NH), 12.46 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 103.5, 117.4, 120.4, 122.5, 124.5, 132.8, 134.1, 152.2 (C quat arom), 99.6, 107.0, 112.1, 113.8, 114.5, 115.8 (C tert arom), 166.4, 169.4 (C=O).

4.1.27. 5-Hydroxy-2-methyl-pyrrolo[3′,4′:5,6]indolizino-[8,7-*b*]indole-1,3-(2*H*,8*H*)-dione (29). Identical procedure as for **20** gave from **19** (59 mg, 0.191 mmol) and Pd black (21 mg, 0.198 mmol) compound **29** (10 mg, 0.033 mmol, 17% yield) as a red solid. Mp 192 °C. IR (KBr) $\nu_{C=O}$ 1700, 1750 cm^{-1}, ν_{NH} 3350–3420 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{17}H_{12}N_3O_3$, 306.0878, found 306.0872. ^1H NMR (400 MHz, DMSO-d_6): 3.12 (3H, s, NCH_3), 6.93 (1H, dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz), 7.05 (1H, m), 7.09 (1H, m), 7.45 (1H, d, J = 8.6 Hz), 8.00 (1H, d, J = 2.3 Hz), 8.25 (1H, m), 9.26 (1H, s, OH), 12.44 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.5 (NCH_3), 99.6, 106.9, 112.2, 113.8, 114.6, 115.9 (C tert arom), 103.6, 116.6, 120.0, 122.4, 124.3, 132.8, 133.9, 152.2 (C quat arom), 165.2, 168.2 (C=O).

4.1.28. 1-Methyl-3-[1-(*tert*-butyl-carboxylate)-1*H*-indol-3-yl]-4-1*H*-pyrrole-2,5-dione (30). To a stirred solution of pyrrole (100 mg, 1.493 mmol) in THF (3 mL) at 0 °C was added dropwise a 2 M solution of EtMgBr in THF (747 μL, 1.493 mmol). The mixture was allowed to reach room temperature before dropwise addition of a solution of **A** (224 mg, 0.553 mmol) in THF (6 mL). The mixture was stirred at room temperature for 24 h before hydrolysis with saturated aqueous NH_4Cl. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed, and the residue purified by flash chromatography using silica gel neutralized with Et_3N (eluent: EtOAc/cyclohexane 1:4 with 1% NEt_3) to give **30** (169 mg, 0.432 mmol, 78% yield) as a red-orange solid. Mp 82–83 °C. IR (KBr) $\nu_{C=O}$ 1700–1740 cm^{-1}, ν_{NH} 3400 cm^{-1}. ^1H (400 MHz, $CDCl_3$): 1.68 (9H, s, CH_3*t*-Bu), 3.20 (3H, s, NCH_3), 6.18 (1H, m), 6.40 (1H, s), 7.05 (1H, s), 7.14–7.22 (2H, m), 7.38 (1H, dt, J_1 = 6.3 Hz, J_2 = 2.2 Hz), 7.95 (1H, s), 8.29 (1H, d, J = 8.2 Hz), 10.47 (1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 24.2 (NCH_3), 28.3 (CH_3 of *t*-Bu), 84.5 (C quat of *t*-Bu), 111.2, 115.6, 117.6, 121.9, 122.7, 123.6, 124.9, 127.6 (C tert arom), 109.5, 118.7, 122.9, 127.0 (2C), 135.6 (C quat arom), 149.2 (C=O Boc), 171.5, 172.8 (C=O).

4.1.29. 2-Methyl-7-(*tert*-butyl-carboxylate)-4,7-dihydro-1*H*-dipyrrolo[3,2-*a*:3,4-*c*]carbazole-1,3-(2*H*)-dione (31). A solution of **30** (80 mg, 0.204 mmol) in acetonitrile (10 mL) was irradiated with a halogen lamp (500 W) for 31 h with cooling to room temperature. The solvent was removed and the residue purified by flash chromatography using silica gel neutralized with Et_3N (eluent: EtOAc/cyclohexane 3:7 with 1% NEt_3) to give **31** (69 mg, 0.177 mmol, 87% yield) as a yellow solid. Mp 172 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1690, 1740, 1760 cm^{-1}, ν_{NH} 3300 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{22}H_{20}N_3O_4$ 390.1454, found 390.1448. ^1H NMR (400 MHz, DMSO-d_6): 1.80 (9H, s, 3 CH_3*t*-Bu), 3.18 (3H, s, NCH_3), 7.21 (1H, d, J = 3.3 Hz), 7.52 (1H, t, J = 7.3 Hz), 7.62 (1H, t, J = 7.3 Hz), 7.72 (1H, d, J = 2.4 Hz), 8.19 (1H, d, J = 7.9 Hz), 9.17 (1H, d, J = 7.9 Hz), 12.25 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.6 (NCH_3), 27.7 (CH_3*t*-Bu), 85.2 (C quat *t*-Bu), 104.4, 114.7, 123.4, 123.7, 127.1, 129.7 (C tert arom), 112.4, 113.8, 119.3, 120.6, 123.6, 129.4, 134.9, 138.1 (C quat arom), 149.8 (C=O Boc), 168.3, 169.4 (C=O).

4.1.30. 2-Methyl-4,7-dihydro-1*H*-dipyrrolo[3,2-*a*:3,4-*c*]carbazole-1,3-(2*H*)-dione (32). Compound **31** (64 mg, 0.164 mmol) was dissolved in formic acid (40 mL). After stirring for 16 h at room temperature, the solution was neutralized by dropwise addition of Et_3N. After addition of saturated aqueous $NaHCO_3$ and extraction with EtOAc, the organic phase was washed with brine then dried over $MgSO_4$. The solvent was removed and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane 3:7) to give **32** (36 mg, 0.124 mmol, 76% yield) as an orange solid. Mp 292 °C. IR (KBr) $\nu_{C=O}$ 1660, 1740 cm^{-1}, ν_{NH} 3320, 3380 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{17}H_{12}N_3O_2$ 290.0930, found 290.0924. ^1H NMR (400 MHz, DMSO-d_6): 3.16 (3H, s, NCH_3), 7.02 (1H, s), 7.32 (1H, t, J = 7.2 Hz), 7.49 (1H, t, J = 7.0 Hz), 7.64 (2H, m), 8.90 (1H, d, J = 8.0 Hz), 12.11 (1H, s, NH), 12.32 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (NCH_3), 100.1, 111.2, 119.8, 123.4, 125.6, 128.8 (C tert arom), 108.4, 110.3, 117.7, 120.8, 121.6, 127.8, 137.5, 140.0 (C quat arom), 169.1, 170.2 (C=O).

4.1.31. 3-(1*H*-Imidazol-1-yl)-1-methyl-4-(1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)-1*H*-pyrrol-2,5-dione (34). A solution of EtMgBr was prepared from magnesium (85 mg) and ethyl bromide (259 µL) in THF (2 mL) then a solution of imidazole (238 mg, 3.50 mmol) in THF (10 mL) was added dropwise at 0 °C. The solution was allowed to reach room temperature then a solution of **33** (530 mg, 1.31 mmol) in THF (23 mL) was added dropwise. The mixture was stirred at 50 °C for 15 h before addition of saturated aqueous NH_4Cl. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, the solvent was removed, and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane 3:7 to 100% EtOAc) to give **34** (343 mg, 1.17 mmol, 90% yield) as a yellow solid. Deprotected starting material (28 mg) was recovered. Physical and spectral data of compound **34** are given in Ref. 17.

4.1.32. 3-(1*H*-Imidazol-1-yl)-1-methyl-4-(1-*tert*-butyl-carboxylate-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-1*H*-pyrrole-2,5-dione (35). To a solution of **34** (330 mg, 1.13 mmol) in THF (30 mL) at 0 °C were successively added catalytic amounts of DMAP and di-*tert*-butyldicarbonate (296 µL, 1,35 mmol). The mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was purified by flash chromatography using silica gel neutralized with Et_3N (eluent containing 1% NEt_3: EtOAc/cyclohexane 1:1 to EtOAc) to give **35** (256 mg, 0.67 mg, 60% yield) as a yellow solid. Starting product **34** (52 mg, 0.177 mmol) was recovered. Mp 144–145 °C. IR (KBr) $\nu_{C=O}$ 1720, 1740, 1780 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{20}H_{20}N_5O_4$ 394.1515, found 394.1516. ^1H NMR (400 MHz, DMSO-d_6): 1.68 (9 H, s, CH_3*t*-Bu), 3.10 (3H, s, NCH_3), 6.87 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz), 7.10 (1H, s), 7.17 (1H, dd, J_1 = 7.9 Hz, J_2 = 4.8 Hz), 7.39 (1H, d, J = 1.2 Hz), 7.96 (1H, s), 8.23 (1H, s), 8.45 (1H, dd, J_1 = 4.7 Hz, J_2 = 1.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 24.2 (NCH_3), 27.1 (CH_3*t*-Bu), 84.7 (C quat *t*-Bu), 104.5, 119.6, 120.0, 129.9, 137.8, 147.0 (C quat arom), 119.2, 119.7, 128.6, 129.5, 130.1, 145.5 (C tert arom), 147.1 (C=O Boc), 166.6, 168.7 (C=O). The tertiary carbon between the two imidazolic nitrogens appears as a quaternary carbon due to a high $^{13}C—^1H$ coupling constant.

4.1.33. 6-Methyl-7a,10-dihydroimidazo[1,2-*a*](1-*tert*-butyl-carboxylate)-pyrrolopyridinylpyrrolo[2,3-*c*:3,4-*e*]pyridine-5,7-dione 36 and 6-methyl-7a,10-dihydroimidazo[1,5-*a*](1-*tert*-butyl carboxylate)-pyrrolopyridinylpyrrolo[2,3-*c*:3,4-*e*]pyridine-5,7-dione (37). A solution of **35** (120 mg, 0.305 mmol) in acetonitrile (7 mL) was irradiated with a halogen lamp (500 W) for 6 h with cooling to room temperature. After removal of the solvent, the residue was purified by flash chromatography using silica gel neutralized with Et_3N (eluent with 1% NEt_3: THF/toluene 3:7 to THF) to give **36** (38 mg, 0.097 mmol, 32% yield) and **37** (44 mg, 0.112 mmol, 37% yield) as off-white solids.

Compound **36**. Mp 270 °C. IR (KBr) $\nu_{C=O}$ 1720, 1750 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 1.64 (9H, s, CH_3, *t*-Bu), 2.94 (3H, s, NCH_3), 5.03 (1H, d, J = 9.2 Hz), 5.87 (1H, d, J = 10.6 Hz), 7.23 (1H, s), 7.40 (1H, dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz), 7.64 (1H, s), 8.40 (1H, d, J = 7.8 Hz), 8.42 (1H, d, J = 4.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 25.3 (NCH_3), 27.2 (3C)(CH_3, *t*-Bu), 38.9, 55.0 (CH), 85.1 (*C*—CH_3, *t*-Bu), 105.5, 118.4, 124.0, 134.5, 147.5 (C quat arom), 118.8, 121.7, 129.4, 129.7, 145.3 (C tert arom), 148.3 (C=O Boc), 173.3, 174.3 (C=O).

Compound **37**. Mp 152 °C. IR (KBr) $\nu_{C=O}$ 1720, 1750 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{20}H_{20}N_5O_4$ 394.1515, found 394.1519. ^1H NMR (400 MHz, DMSO-d_6): 1.69 (9H, s, CH_3, *t*-Bu), 2.91 (3H, s, NCH_3), 4.95 (1H, d, J = 9.4 Hz), 5.93 (1H, d, J = 9.6 Hz), 7.38 (1H, dd, J_1 = 7.9 Hz, J_2 = 4.7 Hz), 7.44 (1H, s), 8.15 (1H, s), 8.38 (1H, d, J = 7.9 Hz), 8.41 (1H, dd, J_1 = 4.6 Hz, J_2 = 1.3 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 25.3 (NCH_3), 27.5 (3C)(CH_3, *t*-Bu), 39.5, 53.1 (CH), 85.0 (*C*—CH_3, *t*-Bu), 103.3, 119.4, 124.9, 139.5, 148.2 (C quat arom), 116.3, 119.1,

128.6, 129.2, 144.8 (C tert arom), 148.7 (C=O Boc), 173.5, 173.9 (C=O).

4.1.34. 6-Methyl-imidazo[1,2-*a*]pyrrolopyridinylpyrrolo[2,3-*c*:3,4-*e*]pyridine-5,7-dione (38). To a solution of **36** (32 mg, 0.081 mmol) in CH_2Cl_2 (5 mL) was added MnO_2 (46 mg, 0.478 mmol). The mixture was stirred at room temperature for 12 h then filtered over Celite. The solid was washed with CH_2Cl_2 then methanol. The filtrate was evaporated to give a yellow solid (31 mg, 0.079 mmol) which was dissolved in formic acid (40 mL). After stirring at room temperature for 12 h, the solution was evaporated, the solid residue was washed with water then EtOAc to give **38** (18 mg, 0.062 mmol, 77% yield) as a yellow solid. Physical and spectral data of compound **38** are given in Ref. 17.

4.1.35. 6-Methyl-imidazo[1,5-*a*]pyrrolopyridinylpyrrolo-[2,3-*c*:3,4-*e*]pyridine-5,7-dione (39). Identical procedure as described for **38** gave from **37** (47 mg, 0.119 mmol) compound **39** (16 mg, 0.055 mmol, 47% yield) as a red solid. Physical and spectral data of compound **39** are given in Ref. 17.

4.1.36. 3-(1*H*-Imidazol-1-yl)-1-methyl-4-[1-(2,3,4,6 tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione 40 and 3-(1*H*-imidazol-1-yl)-1-methyl-4-[7-(2,3,4,6 tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (40a). To a solution of **34** (100 mg, 0.341 mmol) in THF (11 mL) were added 2,3,4,6-*O*-acetylglucopyranose (263 mg, 0.756 mmol) and triphenylphosphine (199 mg, 0.756 mmol). The mixture was cooled to −78 °C then DEAD (120 µL, 0.756 mmol) was added dropwise. The mixture was allowed to reach room temperature with stirring and then was stirred at room temperature for 15 h. After addition of water (50 mL), then extraction with EtOAc, the organic phase was dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (eluent: EtOAc/cyclohexane 3:7 to 100% EtOAc) to give **40** (139 mg, 0.223 mmol, 65% yield) as a yellow solid and **40a** (50 mg, 0.080 mmol, 24% yield) as an orange solid.

Compound **40**. Mp 88–90 °C. IR (KBr) $\nu_{C=O}$ 1710, 1750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.58 (3H, s, CH_3CO), 1.99 (6H, s, CH_3CO), 2.06 (3H, s, CH_3CO), 3.14 (3H, s, NCH_3), 4.06 (1H, m), 4.15 (1H, d, J = 12.4 Hz), 4.28 (1H, dd, J_1 = 12.6 Hz, J_2 = 4.7 Hz), 5.27 (1H, m), 5.48–5.50 (2H, m), 6.26 (1H, d, J = 8.9 Hz, $H_{1'}$), 6.66 (1H, d, J = 7.4 Hz), 6.94 (1H, dd, J_1 = 8.8 Hz, J_2 = 4.7 Hz), 7.09 (1H, s), 7.21 (1H, s), 7.83 (1H, s), 8.17 (1H, s), 8.28 (1H, d, J = 5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 19.9, 20.5, 20.7, 21.0 (CH_3CO), 24.4 (NCH_3), 61.6 ($C_{6'}$), 67.9, 70.8, 72.8, 74.9, 80.3 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 103.1, 117.6, 122.1, 126.4, 137.6, 147.8 (C quat arom), 118.5, 129.2, 130.1, 130.2, 144.6 (C tert arom), 166.7, 168.8 (2C), 169.4, 169.8, 170.5 (C=O).

Compound **40a**. Mp 81–83 °C. IR (KBr) $\nu_{C=O}$ 1710, 1750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.58 (3H, s, CH_3CO), 2.01 (3H, s, CH_3CO), 2.09 (6H, s, CH_3CO), 3.17 (3H, s, NCH_3), 4.18 (2H, m), 4.36 (1H, dd, J_1 = 12.7 Hz, J_2 = 5.0 Hz), 5.27 (1H, t, J = 9.8 Hz), 5.37 (1H, t, J = 8.6 Hz), 5.59 (1H, t, J = 9.5 Hz), 6.98 (1H, t, J = 7.0 Hz), 6.99 (1H, d, J = 8.9 Hz, $H_{1'}$), 7.11 (1H, d, J = 7.0 Hz), 7.15 (1H, br s), 7.17 (1H, br s), 7.83 (1H, s), 8.00 (1H, d, J = 7.1 Hz), 8.55 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 19.9, 20.5, 20.6, 20.7 (CH_3CO), 24.3 (NCH_3), 61.6 ($C_{6'}$), 67.8, 71.6, 72.3, 75.6, 84.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 112.6, 119.3, 127.0, 130.2, 134.5, 152.1 (C tert arom), 103.9, 121.7, 126.4, 126.9, 137.6, 151.0 (C quat arom), 167.5, 169.0, 169.5 (2C), 170.4 (C=O).

4.1.37. 6-Methyl-12-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-imidazo[1,2-*a*] pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-5,7-(6*H*,12*H*)-dione 41 6-methyl-12-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-7a,12-dihydroimidazo[1,2-*a*]pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-5,7-(4a*H*,6*H*)-dione 42 2-methyl-8-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-8,12-dihydroimidazo[1,5-*a*]pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-1,3-(2*H*,3a*H*)-dione (43). A solution of **40** (130 mg, 0.208 mmol) in acetonitrile (10 mL) was irradiated with a halogen lamp (500 W) for 6h with cooling. The solvent was removed and the residue purified by flash chromatography (eluent : EtOAc/cyclohexane 3:7 to 100% EtOAc) to give **41** (6 mg, 9.66 µmol, 5% yield) as a yellow solid, **42** (64 mg, 0.103 mmol, 50% yield) as a salmon-colored solid, and **43** (23 mg, 0.037 mmol, 18% yield) as a pale yellow solid.

Compound **41**. HRMS (FAB+) ($M+H^+$) calcd for $C_{29}H_{28}N_5O_{11}$ 622.1785, found 622.1803. ^1H NMR (400 MHz, $CDCl_3$) (mixture of 2 conformers in 1:1 ratio): 1.55 (3H, s, CH_3CO), 1.58 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CO), 2.01 (3H, s, CH_3CO), 2.09 (3H, s, CH_3CO), 2.12 (6H, s, CH_3CO), 2.14 (3H, s, CH_3CO), 3.29 (6H, s, CH_3), 4.10–4.32 (6H, m), 5.52-5.66 (3H, m), 5.90 (1H, t, J = 9.7 Hz), 6.86 (1H, d, J = 9.3 Hz), 7.12 (1H, t, J = 9.4 Hz), 7.14 (1H, t, J = 9.2 Hz), 7.42 (1H, dd, J_1 = 7.0 Hz, J_2 = 5.3 Hz), 7.44 (1H, dd, J_1 = 7.4 Hz, J_2 = 5.8 Hz), 7.76 (1H, d, J = 9.4 Hz), 7.94 (1H, s), 8.07 (1H, s), 8.59 (2H, dd, J_1 = 5.5 Hz, J_2 = 1.2 Hz), 8.62 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz), 8.65 (1H, dd, J_1 = 4.7 Hz, J_2 = 1.4 Hz), 9.04 (1H, d, J = 7.6 Hz), 9.12 (1H, dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz). *Compound* **42**. Mixture of 4 isomers. HRMS (FAB+) ($M+H^+$) calcd for $C_{29}H_{30}N_5O_{11}$ 624.1942, found 624.1943. *Compound* **43**. mixture of 2 isomers in 1:1 ratio. ^1H NMR(400 MHz, $CDCl_3$): 1.27 (3H, s, CH_3CO), 1.31 (3H, s, CH_3CO), 1.93 (3H, s, CH_3CO), 2.00 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 2.09 (3H, s, CH_3CO), 2.26 (3H, s, CH_3CO), 2.30 (3H, s, CH_3CO), 3.02 (3H, s, CH_3), 3.04 (3H, s, CH_3), 4.12 (2H, m), 4.24 (1H, d, J = 12.7 Hz), 4.32 (1H, d, J = 13.0 Hz), 4.36 (1H, d, J = 13.0 Hz), 4.45 (1H, d, J = 12.7 Hz), 4.72 (1H, d, J = 9.0 Hz), 4.80 (1H, d, J = 9.9 Hz), 5.47 (5H, m), 5.57 (3H, m), 6.53 (1H, d, J = 5.3 Hz), 6.68 (1H, d, J = 9.0 Hz), 7.12–7.20 (2H, m), 7.89 (1H, s), 7.95 (1H, s), 7.99 (1H, s), 8.09 (1H, s), 8.27–8.36 (4H, m).

4.1.38. 2-Methyl-8-(2,3,4,6-tetra-*O*-acetyl-β-D-lucopyranosyl)-imidazo[1,5-*a*]pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-1,3-(2*H*,8*H*)-dione (43a). To a solution of **43** (38 mg, 0.061 mmol) in CH_2Cl_2 (5 mL)

was added MnO_2 (34 mg, 0.391 mmol). The mixture was stirred at room temperature for 48 h, filtered over Celite. The solid was washed with CH_2Cl_2 and EtOAc. The filtrate was evaporated. The residue was purified by flash chromatography (eluent: EtOAc/cyclohexane 1:1) to give **43a** (23 mg, 0.037 mmol, 61% yield) as a red solid. Mp 204 °C. IR (KBr) $\nu_{C=O}$ 1710, 1720, 1750, 1760 cm^{-1}. HRMS (FAB+) ($M+H^+$) calcd for $C_{29}H_{28}N_5O_{11}$ 622.1785, found 622.1779. ^1H NMR (400 MHz, $CDCl_3$): 1.27 (3H, s, CH_3CO), 2.00 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO), 2.31 (3H, s, CH_3CO), 3.26 (3H, s, NCH_3), 4.26 (1H, d, J = 9.4 Hz), 4.35 (1H, d, J = 12.7 Hz), 4.46 (1H, dd, J_1 = 12.6 Hz, J_2 = 2.0 Hz), 5.60–5.76 (3H, m), 6.88 (1H, d, J = 9.2 Hz, $H_{1'}$), 7.40 (1H, dd, J_1 = 7.9 Hz, J_2 = 4.8 Hz), 8.47 (1H, s), 8.52 (1H, dd, J_1 = 4.6 Hz, J_2 = 1.0 Hz), 8.99 (1H, d, J = 7.8 Hz), 9.12 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 19.5, 20.7 (2C), 21.0 (CH_3CO), 24.1 (NCH_3), 60.9 ($C_{6'}$), 67.5, 69.6, 72.9, 75.5, 81.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.3 (2C), 132.1 (2C), 145.8 (C tert arom), 105.2, 114.4, 130.2 (2C), 150.1 (C quat arom), 164.3, 167.3, 168.6, 169.3, 170.0, 170.8 (C=O).

4.1.39. 6-Methyl-12-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-imidazo[1,2-*a*]pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-5,7-(6*H*,12*H*)-dione 41 from 42. Identical procedure as described above for the preparation of **43a** from **43** gave from **42** (60 mg, 0.096 mmol) and MnO_2 (53 mg, 0.61 mmol) compound **41** (48 mg, 0.077 mmol, 80% yield) as a yellow solid.

4.1.40. 6-Methyl-12-(1-β-D-glucopyranosyl)-imidazo[1,2-*a*]-pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-5,7-(6H,12H)-dione (44). To a solution of compound **41** (55 mg, 0.088 mmol) in methanol (4 mL) was added dropwise 1 M NaOMe in MeOH (20 μL). The mixture was stirred at room temperature for 12 h. The solvent was removed. The solid was washed with methanol to give **44** (20 mg, 0.044 mmol, 50% yield) as a yellow solid. Physical and spectral data of compound **44** are given in Ref. 17.

4.1.41. 2-Methyl-8-(β-D-glucopyranosyl)-imidazo[1,5-*a*]pyrido[3′,2′:4,5]pyrrolo[2,3-*c*]pyrrolo[3,4-*e*]pyridine-1,3-(2*H*,8*H*)-dione (45). Identical procedure as described for **44** gave from **43a** (20 mg, 0.032 mmol) compound **45** (6 mg, 0.013 mmol, 42% yield) as a red solid. Physical and spectral data of compound **45** are given in Ref. 17.

4.2. Kinases inhibition assays

Human Chk1 full-length enzyme with an N-terminal GST sequence was either purchased from Upstate Biochemicals (No. 14–346) or purified from extracts of Sf9 cells infected with a baculovirus encoding GST–Chk1. Assays for compound testing were based upon the method described by Davies et al.[37]

Src inhibition assays: Inhibitors were diluted with a Tecan Evo150 robot. The kinase assay was performed with 4 μL of inhibitor (10%DMSO), 10 μL of kinase assay buffer 4× concentrated (80 mM $MgCl_2$, 200 mM HEPES, 0.4 mM EDTA, 2 mM DTT), 10 μL substrate peptide (KVEKIGEGYYGVVYK, 370 nM), and 6 μL Src kinase (stock GTP purified diluted with 1× kinase assay buffer to 200 nM). 10 μL co-substrate (40 μM ATP with 0.2 μCi P^{33}-γ-ATP) was added with a Precision 2000 (Biotek Robotic). The assay was incubated for 20 min at 30 °C then stopped by adding 200 μL of 0.85% orthophosphoric acid, then transferred to a phosphocellulose filter microplate (Whatman—P81). The plate was washed three times with 200 μL of 0.85% orthophosphoric acid dried with 200 μL acetone. The remaining activity was measured on a Topcount with 25 μL scintillation solution (Packard UltimaGold).

Inhibition assays toward other kinases were performed by Upstate's kinase profiler screening service.

4.3. Growth inhibition assays

Tumor cells were provided by American Type Culture Collection (Frederik, MD, USA). They were cultivated in RPMI 1640 medium (Life Science technologies, Cergy-Pontoise, France) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin, and 10 mM HEPES buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay as described.[38] Cells were continuously exposed to graded concentrations of the compounds for four doubling times, then 15 μL of 5 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was added to each well and the plates were incubated for 4 h at 37 °C. The medium was then aspirated and the formazan solubilized by 100 μL of DMSO. Results are expressed as IC_{50}, concentration which reduced by 50% the optical density of treated cells with respect to untreated controls.

4.4. DNA binding and topoisomerase I inhibition

DNA interaction and topoisomerase I inhibition were evaluated according to previously published procedures.[39,40]

References and notes

1. Zhou, B.-B.; Elledge, S. J. *Nature* **2000**, *408*, 433–439.
2. Nyberg, K. A.; Michelson, R. J.; Putnam, C. W.; Weinert, T. A. *Annu. Rev. Genet.* **2002**, *36*, 617–656.
3. Cuddihy, A. R.; O'Connell, M. J. *Int. Rev. Cytol.* **2003**, *222*, 99–140.
4. Abraham, R. T. *Genes Dev.* **2001**, *15*, 2177–2196.
5. Meijer, L. *Oncologie* **2003**, *5*, 311–326.
6. Molinari, M. *Cell Prolif.* **2000**, *33*, 261–274.
7. Chen, Z.; Xiao, Z.; Chen, J.; Ng, S.-C.; Sowin, T.; Sham, H.; Rosenberg, S.; Fesik, S.; Zhang, H. *Mol. Cancer Ther.* **2003**, *2*, 543–548.
8. Graves, P. R.; Yu, L.; Schwaz, J. K.; Gales, J.; Sausville, E. A.; O'Connor, P. M.; Piwnica-Worms, H. *J. Biol. Chem.* **2000**, *275*, 5600–5605.
9. Zhao, B.; Bower, M. J.; McDevitt, P. J.; Zhao, H.; Davis, S. T.; Johanson, K. O.; Green, S. M.; Concha, N. O.; Zhou, B.-B. S. *J. Biol. Chem.* **2002**, *277*, 46609–46615.

10. Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 9850–9856.
11. Roberge, M.; Berlinck, R. G. S.; Xu, L.; Anderson, H. J.; Lim, L. Y.; Curman, D.; Stringer, C. M.; Friend, S. H.; Davies, P.; Vincent, I.; Haggarty, S. J.; Kelly, M. T.; Britton, R.; Piers, E.; Andersen, R. *J. Cancer Res.* **1998**, *58*, 5701–5706.
12. Andersen, R. J.; Roberge, M.; Sanghera, J.; Leung, D. International Patent, WO99/47522, CA 131:243451, 1999.
13. Jiang, X.; Zhao, B.; Britton, R.; Lim, L. Y.; Leong, D.; Sanghera, J. S.; Zhou, B. B. S.; Piers, E.; Andersen, R.; Roberge, M. *Mol. Cancer Ther.* **2004**, *3*, 1221–1227.
14. Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530–535.
15. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 3935–3937.
16. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 3927–3930.
17. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607–4611.
18. Hénon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 5599–5614.
19. Hénon, H.; Anizon, F.; Kucharczyck, N.; Loynel, A.; Casara, P.; Pfeiffer, B.; Prudhomme, M. *Synthesis* **2006**, 711–715.
20. Bush, J. A.; Long, B. H.; Catino, J. J.; Bradner, W. T.; Tomita, K. *J. Antibiot.* **1987**, *40*, 668–678.
21. Bailly, C.; Riou, J.-F.; Colson, P.; Houssier, C.; Rodrigues-Pereira, E.; Prudhomme, M. *Biochemistry* **1997**, *36*, 3917–3929.
22. Bailly, C.; Colson, P.; Houssier, C.; Rodrigues-Pereira, E.; Prudhomme, M.; Waring, M. J. *Mol. Pharmacol.* **1998**, *53*, 77–87.
23. Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron Lett.* **2006**, *47*, 433–436.
24. Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096–1097.
25. Bocchi, V.; Palla, G. *Tetrahedron* **1984**, *40*, 3251–3256.
26. Barry, J. F.; Wallace, T. W.; Walshe, N. D. A. *Tetrahedron* **1995**, *51*, 12797–12806.
27. Desarbre, E.; Bergman, J. *J. Chem. Soc., Perkin Trans I* **1998**, 2009–2016.
28. Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887–2892.
29. Terpin, A.; Winklhofer, C.; Schumann, S.; Steglich, W. *Tetrahedron* **1998**, *54*, 1745–1752.
30. Routier, S.; Ayerbe, N.; Mérour, J.-Y.; Coudert, G.; Bailly, C.; Pierré, A.; Pfeiffer, B.; Caignard, D.-H.; Renard, P. *Tetrahedron* **2002**, *58*, 6621–6630.
31. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 679–687.
32. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem.* **2003**, *46*, 609–622.
33. Bayle, C.; Defaye, J.; Horton, D.; Lehman, J.; Scheuring, M. *Carbohydr. Res.* **1992**, *232*, 375–380.
34. http://www.aist.go.jp/RIODB/SDBS/menu-e.html.
35. Bailly, C.; Qu, X.; Anizon, F.; Prudhomme, M.; Riou, J. F.; Chaires, J. B. *Mol. Pharmacol.* **1999**, *55*, 377–385.
36. Gray, N.; Détivaud, L.; Doerig, C.; Meijer, L. *Curr. Med. Chem.* **1999**, *6*, 859–875.
37. Davies, S. P.; Reddy, H.; Caivano, M.; Cohen, P. *Biochem. J.* **2000**, *351*, 95–105.
38. Léonce, S.; Pérez, V.; Casabianca-Pignède, M. R.; Anstett, M.; Bisagni, E.; Atassi, G. *Invest. New Drugs* **1996**, *14*, 169–180.
39. Anizon, F.; Moreau, P.; Sancelme, M.; Laine, W.; Bailly, C.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 3709–3722.
40. Voldoire, A.; Moreau, P.; Sancelme, M.; Matulova, M.; Léonce, S.; Pierré, A.; Hickman, J.; Pfeiffer, B.; Renard, P.; Dias, N.; Bailly, C.; Prudhomme, M. *Bioorg. Med. Chem.* **2004**, *12*, 1955–1962.